A.M.A. Journal OF

DISEASES OF CHILDREN

The Ehlers-Danlos Syndrome — *George K. Summer*

Muscular Dystrophy

V. Blood Sugar and Serum Electrolytes Following Insulin and Dextrose, Alone or in Combination
T. S. Danowski, H. K. Gillespie, T. J. Egan, F. M. Mateer, and M. H. Leinberger

VI. Diminished Blood Sugar and Serum Electrolyte Responses to Epinephrine
E. B. Fergus, W. R. Nichols, L. M. Horne, and T. S. Danowski

VII. Trials of a Pituitary Growth Factor
T. S. Danowski, L. Greenman, F. M. Mateer, M. J. Wratney, and J. S. Donaldson

VIII. Trials of Protein Hydrolysate, Vitamin Supplements, and Physical Therapy
J. S. Donaldson, M. J. Wratney, A. Pascussio, F. A. Weigand, and T. S. Danowski

Prednisone in the Treatment of Allergic Disorders in Children
Sheldon C. Siegel, Victor Bienberg, and Vincent C. Kelley

An Attempt to Elucidate the Cause of Growth Retardation in Renal Disease
Clark D. West and William C. Smith

Tuberculous Meningitis in Children — *Gladys Boyd*

Complete Contents on First Inside Page

MAY 1956

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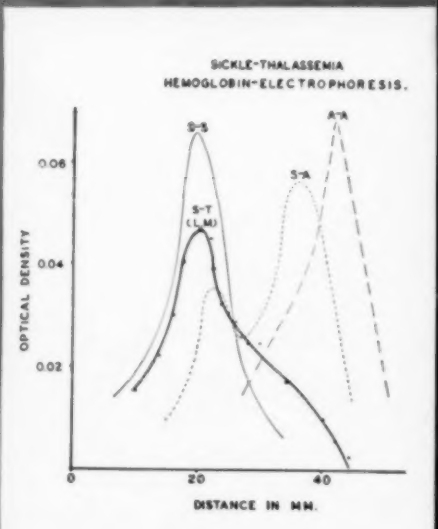
From Shields et al., p. 483



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A. M. A.
Journal of Diseases of Children

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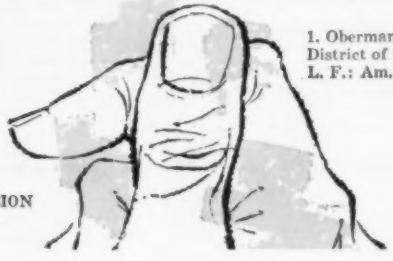

1. Oberman, J. W., and Burke, F. G.: M. Ann. District of Columbia 23:483, 1954. 2. Hill, L. F.: Am. J. Clin. Nutrition 3:75, 1955.

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1. Bair, H.V., and Herold, W.: Arch. Neurol. & Psychiat. *74*:363 (Oct.) 1955.
2. Brooks, G.W.: in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.

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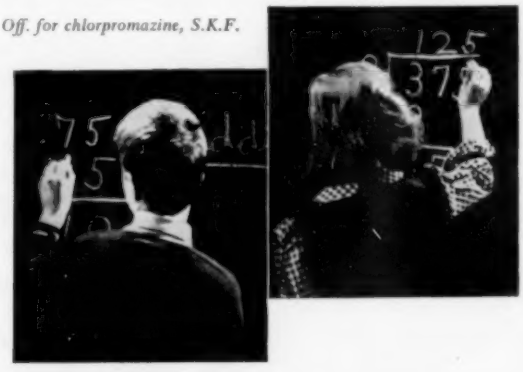

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13-15 yrs., 108 lb., 63 in.	80 Gm.	**Women**	
16-20 yrs., 120 lb., 64 in.	75 Gm.	25-65 yrs., 121 lb., 62 in.	55 Gm.

1. Recommended Dietary Allowances, Report of the Food and Nutrition Board, National Academy of Sciences—National Research Council, Publication 302, Washington, D.C., 1953.
2. Brock, J. F., and Autret, M.: Kwashiorkor in Africa, Bull. World Health Organ. *5*:1 (1952).
3. McLester, J. S., and Darby, W. T.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, p. 218.

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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The Ehlers-Danlos Syndrome

A Review of the Literature and Report of a Case with a Subgaleal Hematoma and Bell's Palsy

GEORGE K. SUMMER, M.D., Chapel Hill, N. C.

Edvard Ehlers (1863-1937), a German dermatologist, in 1901 was the first to describe a syndrome which included laxity of the skin and joints associated with a tendency to hemorrhage.[1] In 1907, Paul Cohn recorded a similar syndrome with circumscribed changes in the skin.[2] Henri Alexandre Danlos (1844-1912), a French physician, in 1908 described a syndrome of laxity of the skin with tumors about the elbows and knees resulting from chronic contusions.[3] This case had been reported earlier by Hallopeau as a doubtful form of diabetic xanthomatosis.[4] Since 1908 the symptoms comprising the Ehlers-Danlos syndrome have been characterized by the following features: (1) extreme laxity of the skin (dermatochalasis); (2) extreme laxity of the joints (arthrochalasia); (3) fragility of the skin (dermatorrhexis) and blood vessels. L. M. Pautrier first reported the pathologic findings in the case described by Danlos in 1908.[5] The first American case recorded was that of N. Tobias in 1934.[6]

The occurrence of each feature of the triad and the degree of its prominence vary so that in one particular patient laxity of the skin may be less notable while laxity of the joints is unusually prominent.[7] In other patients, fragility of the skin and blood vessels is more prominent than laxity of the joints and skin. The incomplete cases consisting of cutis laxa or extreme laxity of the joints alone have been classified by some authorities as formes frustes of this syndrome. French authors divide cases into two categories: (1) *peau élastique* and (2) *peau élastique avec laxités articulares*. They note gradations from abortive forms to the complete syndrome.[9] However, the triad of symptoms mentioned must be present in order to fulfill the criteria of the Ehlers-Danlos syndrome.

Other common features of the syndrome are peculiar "pseudotumors" of the connective tissue which develop in the atrophic scars commonly seen in this condition. Freely movable nodules which are pea-sized and slip about under the skin occur in the subcutaneous tissue. Microscopically the nodules have been noted to consist of fat, although from their hardness one would not expect them to be lipomata.

Because of the rarity of this syndrome, a report of the following case seems warranted. When F. Ronchese[10] reviewed the literature in 1936, the total number of published cases was 27; in 1949 the total was less than 50; in 1955 the total is less than 100.

REPORT OF A CASE

An 11-year-old white girl was admitted to the hospital for the first time on Aug. 23, 1953. Ten hours earlier she had fallen, striking the occipital

Received for publication Jan. 5, 1956.

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Fig. 1.—Patient with the Ehlers-Danlos syndrome.

region of her head on the floor. The head began to swell and became ecchymotic over the entire surface of the scalp. By the time of admission the head was the size of a basketball. She became progressively lethargic and vomited twice during this 10-hour period, but at no time did she complain of headache or lose consciousness.

The past history revealed that she had enjoyed fair general health but had always been a frail and weak child. All her life she had bruised easily, and she had been given numerous injections of liver extract and oral iron preparations for anemia. Occasionally she had had bleeding of the gums while brushing her teeth and epistaxis associated with upper respiratory infections. Five months prior to admission she had had hematuria, and a diagnosis of acute glomerulonephritis was made. Recovery was uneventful. The mother of the child had had vaginal bleeding during the second trimester of pregnancy.

The patient was born after a seven-month gestational period, and the birth weight was 3 lb. (1360 gm.). Her joints and skin were noted to be extremely lax at birth. She had developed slowly in infancy, sitting up at 1 year, walking alone at 2 years. During walking, the left hip frequently became dislocated, and she had learned to reduce the dislocation herself. She started school at 8 years of age and has always done well in her work.

Fig. 2A.—Hyperlaxity of the skin of the thigh.

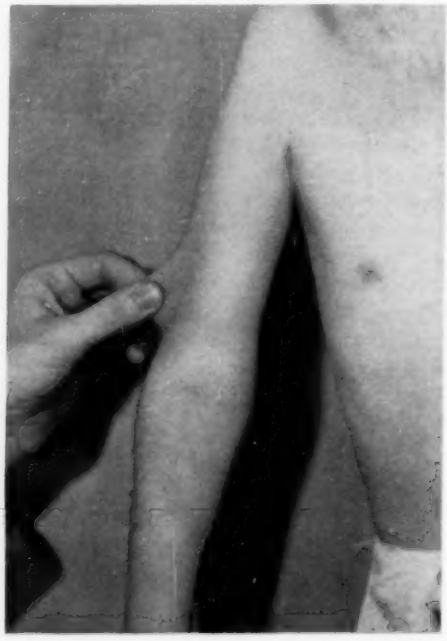


Fig. 2B.—Hyperlaxity of the skin of the upper arm.

Fig. 3.—Patient one year after admission, showing facial scars and recovery from facial palsy.

In the family history there was no evidence of a similar disorder, consanguinity, or blood dyscrasias.

The physical examination revealed a poorly developed, emanciated, pale white girl who appeared acutely and chronically ill (Fig. 1). The temperature was 99 F; pulse rate 140; respirations, 20; blood pressure, 80/60. She was well oriented but restless and irritable.

Fig. 4.—Scarring of the left hand.

The skin was dry and cold, with a loose velvety texture (Figs. 2A and 2B). There were many papery thin scars on the forehead, face, knees, and left hand (Figs. 1, 3, and 4). Scattered bruises were present over the back, knees, and upper arms. The entire head was swollen, edematous, and ecchymotic (Fig. 5). There was a very large fluctuant collection of subgaleal fluid over the posterior aspect of the skull, extending to the temporal region on the left and to the postauricular region on the right. Hearing was normal. The external auditory canals did not show blood or exudate. Examination of the eyes superficially revealed blue sclerae and pupils 3 mm. in diameter, which reacted normally to light and in accommodation. Vision in both eyes was myopic, and there was a slight left esotropia. Extraocular movements and the funduscopic findings were normal. All joints were hyperextensible, especially the metacarpophalangeal joints, the wrists,

Fig. 5.—X-ray of the skull, showing subgaleal hematoma.

and the knees (Figures 6A, 6B, and 6C). The left knee joint was enlarged, but there was no evidence of tenderness, limitation of motion, crepitation, or fluid. The chest was symmetrical, expanding equally bilaterally, and the lungs were clear to auscultation. The heart was not enlarged. Cardiac sounds were normal, and no murmurs or arrhythmias were present. The abdomen was flat and soft. Tenderness and masses were not detectable. The liver, spleen, and kidneys were not palpable. Peristalsis was normal.

The external genitalia were normal. Rectal examination revealed no tenderness or masses.

The limbs and fingers were long and slender. There was slight cyanosis of the nail beds. Peripheral edema and clubbing were not present. The cranial and peripheral motor and sensory functions were normal on the initial examination. Reflexes were equal and active bilaterally. Subsequently the

Fig. 6A.—Hyperextensibility of the joints of the third finger (side view).

Fig. 6B.—Hyperextensibility of the joints of the third finger (front view).

Fig. 6C.—Hyperextensibility of the hand and wrist.

TABLE 1.—*Additional Laboratory Findings*

STS	Negative
CSF examination	Normal
Bone age	11 years (chronological age)
Skull x-rays	No evidence of fracture
Skeletal x-rays	Normal
Prothrombin time	91% of normal (15 min. control)
Bleeding time	Normal
Clotting time	Normal
Clot retraction	Normal
Tourniquet test	Normal

patient developed a left facial palsy. There were no other unilateral or localizing neurological signs.

Laboratory data on admission revealed a hemoglobin value of 6.5 gm. per 100 cc., a red blood cell count of 2,520,000/cu. mm., and a hematocrit value of 21%. These values returned to normal after transfusion. Urinalyses were normal. Other laboratory data are shown in Table 1; these findings are

Fig. 7.—Patient with left facial palsy.

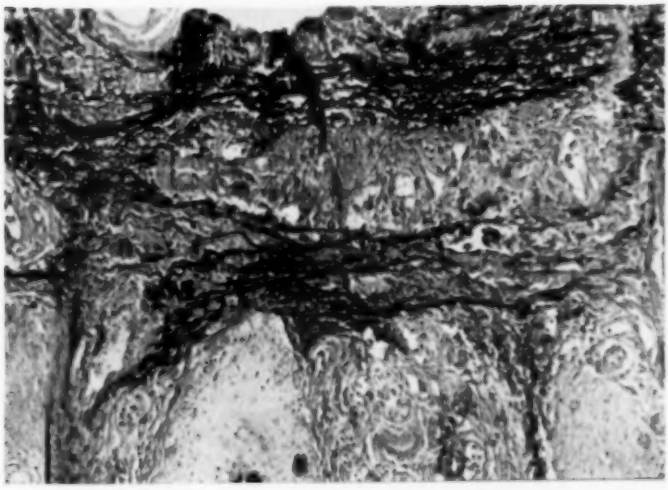


Fig. 8A.—Biopsy specimen of the scalp. The elastic tissue is striking in the stratum reticulare. Verhoeff's stain; reduced from mag. × 100.

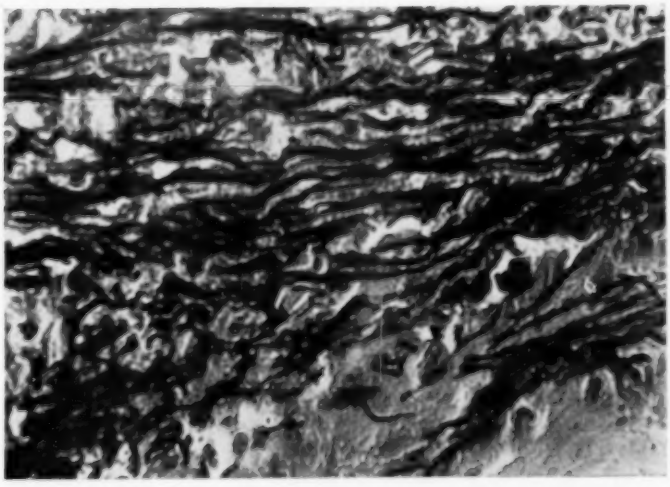


Fig. 8B.—Biopsy specimen of the scalp. The same area as in Figure 8A. Verhoeff's stain; reduced from mag. × 430.

typical of those in patients with the Ehlers-Danlos syndrome.

The hospital course was satisfactory. The patient was given procaine penicillin, 300,000 units i. m. daily, and sulfisoxazole U. S. P. (Gantrisin) tablets, 0.5 gm. orally every six hours. Transfusions which totalled 1500 ml. were given in 250 ml. amounts. Vitamin K (10 mg. I. M. daily) and ascorbic acid (vitamin C) (75 mg. I. M. daily) were given for nine days. The hematoma was evacuated, and the wound healed slowly after suturing. During the first two days in the hospital she developed a left facial palsy, probably due to the extensive hematoma and the resultant pressure on the seventh cranial nerve (Fig. 7). Follow-up visits have shown a gradual improvement in the facial palsy. Subcutaneous bleeding has not recurred, although she has reported rather extensive bruises from minor trauma on the lower legs.

A biopsy was taken of the skin of the patient's scalp. Owing to hemorrhage and pressure necrosis of the skin, the microscopic anatomy was distorted. Special stains for elastic tissue and collagen revealed the former to be increased rather strikingly in some sections (Figs. 8A and 8B). No deficiency or abnormality in collagen was noted.

COMMENT

According to genetic studies, the Ehlers-Danlos syndrome is a hereditary disease of dominant type phenotypically determined by

the action of multiple genes, the effects of which are cumulative. It has been suggested that the phenotypic manifestations of these genes are under hormonal control.[11]

The syndrome has about an equal distribution between the sexes. Frequently there is a familial history, and in some cases there is a history of prematurity. Johnson and Falls reported several cases in which only one prematurely born child in a family had the syndrome. They stated that consanguinity is to be considered strongly as a contributory factor.[12]

Symptoms and signs of the Ehlers-Danlos syndrome are usually present at birth, but the hemorrhagic manifestations and dermal fragility are usually not manifested until the child begins to walk or is otherwise subjected to trauma. The differential diagnosis is not difficult except in the early months, when Mongolism, cretinism, neurofibromatosis, or cutis laxa may present similar symptoms and signs. The Indian rubber men of the circus, with their extreme laxity of the skin and joints, usually do not manifest fragility of the skin and blood vessels; therefore they are not considered as examples of the Ehlers-Danlos syndrome. In many cases the patient grows to young adulthood without a correct diagnosis—usually because the syndrome is not recognized.

Arthrochalasis. — Joint instability causes stumbling and falling and, as a result, joint dislocations, sprains, ecchymoses, and gaping lacerations. Dislocation of the shoulder may follow putting on a coat. The metacarpophalangeal joints may show such laxity and extensibility that the person can touch by extension the dorsum of the wrist with the finger tips. Generalized and bilateral laxity of the temporomaxillary joint and also of the spine has been reported. In the majority of cases the laxity of the joints is most marked in the fingers and thumbs. Apparently the joints are not painful.[6]

The laxity of the joints is as striking as laxity of the skin and is presumably due to an abnormality of the mesodermal tissue in the joint capsule analogous to that of the skin. The elbows, knees, and other large joints may be permanently dislocated. No radiological abnormalities have been demonstrated in the joints.[13]

Other explanations for the laxity of the joints include suggestions that hypertrophy of the elastic fibers in the capsule and ligaments may be responsible.[14] Hypotonia of muscles may also play a role. Collagen sheaths of muscle fibers may be altered, and collagen bundles in ligaments and joint capsules may have a loose structure as in the dermis and hypodermis.[15] The joints have not been studied as thoroughly as the skin, and the explanation for the laxity of the joints in this syndrome remains obscure.

Dermatochalasis. — The skin is usually velvety and dry. Grossly the epidermis appears wrinkled, and sometimes pinching causes slight discomfort. Frequently there is undue sensitiveness to manipulations, such as taking the blood pressure. Some patients report an intensely disagreeable sensation produced by rubbing with a towel.

Pautrier in his original and classical report with Danlos stressed vascular changes and dismissed alterations in the collagen and elastic fibers.[5] Turnbull and Burrows studied the skin in relation to controls and were unable to state definitely if an increase in elastic tissue existed. The depths were identical in the control and in the patient with the "elastic skin." A definite difference was noted in the collagen fibers of the reticular layer of the dermis—the collagen fibers were not packed to form the massive bundles seen in the control. The reticular layer was consequently of looser structure and formed a confused tangle of collagen fibers and other connective tissue elements. The rarefaction of the reticular layer appeared to be due to a deficiency in collagen fibers. Thus the elastic fibers were less evenly spaced than in the control and tended to come together in larger bundles.[16]

There is general agreement in the literature that the pars reticularis is looser than normal and that the elastic tissue is more prominent and occurs in coarser tangled bundles than in normal skin.[17] Recently Jansen has suggested that the elastic tissue

predominates because the quantity of collagen is decreased; thus the increase in elastic tissue may be more relative than absolute.[15] He points out that in normal tissue the papillary layer is composed of very fine collagen fibers, forming a meshwork or wickerwork. The extensibility of the collagen wickerwork depends on the extent to which the fibers glide along each other. Since the papillary layer is firmly attached to the epidermis, its mobility is very limited. The stratum reticulare consists of collagen fibers and fiber-bundles interwoven in a three-dimensional manner, which can be demonstrated by the direction of cleavage lines. The tension of normal skin parallel to these cleavage lines is believed to be maintained by elastic fibers which twist themselves through the collagen wickerwork like an ivy vine. The lower stratum reticulare has a looser structure consisting of fat lobules which separate the collagen fiber-bundles. Another factor in the tensile strength of the skin is the manner in which septa composed of connective tissue, collagen, and elastic tissue run from the stratum reticulare through the hypodermis and attach the overlying skin to muscle and bone.

Jansen's study by electron microscopy of collagen of normal subjects and patients with the Ehlers-Danlos syndrome reveals that both have characteristic cross striations and typical spacing of about 640 A. Also the thickness of the fibrils is uniform in normal subjects and in patients with the syndrome (1200-1600 A.). The fact that the cross striations and spacings of the striations are uniform in both groups suggests a similar molecular and chemical make-up. Observations with the electron microscope reveal no striking difference in the elastic fibers of normal subjects and patients with the Ehlers-Danlos syndrome. Elastic fibers with a diameter of 5000 A. occur with ribbon-like subfibers, a uniform thickness of about 600 A., and no apparent longitudinal periodicity of cross striations.

Therefore, it appears that the collagen wickerwork is the limiting factor in the extensibility of the skin, since one can tear the skin of a patient with the Ehlers-Danlos syndrome loose after circular incision through the dermis, leaving little or no subcutaneous fat at the base of the skin. The degree to which the skin can be extended is dependent on the extent to which the collagen fibers can glide along each other. The attachments of the collagen wickerwork to the epidermis and also to the underlying structures of muscle and bone also limit extensibility. Connective tissue between collagen fibers more or less encases the fibril-bundles of collagen, accounting for the solid coherence of the constituents of the dermis.

Dermatorrhexis. — The numerous large atrophic scars on the exposed portions of the body testify to the third feature of the triad—fragility of the skin. The peculiar fragility of the skin and blood vessels from a dermatologic and practical standpoint is the main feature of the syndrome. Gaping wounds delay healing, and wounds leave broad papyraceous scars when they do heal.

A small cut or incision of the skin may become appreciably wider, longer, and deeper as a result of the edges pulling away from the wound because of the extreme laxity of the skin. Scarring is most prominent over the bony prominences subject to trauma, like the forehead, elbows, knees, and tibial surfaces. The scars are not adherent to the subcutaneous tissue and are not firm like keloids.

Associated with fragility of the skin is vulnerability and fragility of the blood vessels. Large hematomas may occur after blows which in themselves are insufficient to break the surface of the skin. Ecchymoses from pressure on the arm and from performances of the Rumpel-Leede test have occurred.[11] The fragility of the skin has been attributed to the defective collagen wickerwork of the reticular layer of the skin, and as a result the epidermis lacks a good buffer to trauma. Likewise, blood vessels are also more susceptible to trauma, since they do not have the support or buffering of normal

subcutaneous tissue. Microscopically, there is no abnormality of the blood vessel wall.

Other Anomalies Associated with the Ehlers-Danlos Syndrome. — The Ehlers-Danlos syndrome frequently is associated with other anomalies. Shapiro states that the association with intellectual impairment along with other congenital abnormalities is evidence that the entire syndrome is due to a congenital maldevelopment secondary to some embryologic disturbance. A list of anomalies frequently associated with this condition is shown in Table 2.

No definite or constant metabolic abnormality has been disclosed. Dobrosworskaja considered a multiglandular defect, since her patients showed underdevelopment of primary and secondary sexual characteristics.[18] Acrocyanosis and laxity of the joints have been considered attributable to a pituitary dysfunction. Some authors have implicated the parathyroid gland, but the results have been contradictory. Tobias (1934) found the blood calcium well below normal (6.4 mg. per 100 cc.); Raybaud and Guidoni (1938) found the blood calcium slightly increased.[19] Others have found blood calcium to be normal.

TABLE 2.—*Anomalies Associated with the Ehlers-Danlos Syndrome*

Abnormalities of the external ear
Absence of the ensiform process
Achondroplasia
Acrocyanosis
Arachnodactyly
Clinodactyly
Club feet
Congenital cardiac disease
Congenital dislocation of the hip
Congenital muscular atony
Delayed cranial ossification
Diffuse muscular atrophy
Enteroptosis
Gastric atony
Megacolon
Megaesophagus
Mental retardation
Multiple lipomata
Neurofibromatosis
Oligophrenia
Osteogenesis imperfecta
Osteoporosis
Spina bifida
Synostosis of the proximal heads of the radii and ulnae
Thoracic deformities

Kanof suggested a possible relationship between hyperadrenocorticism and the Ehlers-Danlos syndrome. The symptoms and signs in common with hyperadrenocorticism, Cushing's disease, and patients receiving corticotropin or cortisone are dermatorrhexis, delayed healing, fragile blood vessels, weakness, acrocyanosis, osteoporosis, delayed epiphyseal development, increased 17-ketosteroids in the urine, increased uric acid/creatinine ratio in the urine, and, occasionally, eosinopenia.[20] No other reports have indicated a consistent similarity of findings in these diseases.

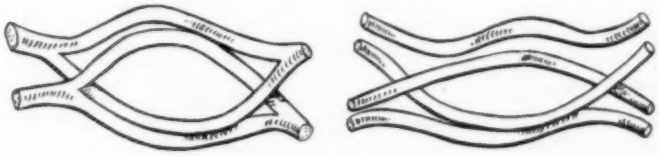
Soft-Tissue Abnormalities. — The small disseminated round discrete calcareous nodules which are described in patients with the Ehlers-Danlos syndrome appear to involve either the skin itself or the immediate underlying tissues and vary from the size of a millet seed to that of a pea. Some of the nodules may be calcified. Holt offers the opinion that trauma, especially of the extensor surfaces, accounts for the presence of necrotic fat and foreign-body giant cells. The calcified nodules superficially resemble the more commonly encountered phleboliths in hemangiomata.

The pseudotumors and sizable angiomata present much the same roentgenographic appearance. Both are associated with minor alterations in normal bone architecture. The pseudotumors of the Ehlers-Danlos syndrome are superficial and contain multiple concentric strata of calcium. Protuberances in the form of pseudotumors occur at the exposed areas such as the elbows and knees. Often the pseudotumors are molluscum-like and have the shape of raisins, covered with a glistening semitranslucent membranous capsule through which may be seen colors varying from deep red to blue, as in hemangiomas.

Summary of Findings.—The etiology heretofore has been ascribed to a congenital dysplasia of the mesenchymal tissue, since ectodermal derivatives such as hair, teeth, and nails are normal. Biopsies of the skin generally show the following features: atrophy of the epidermis, rarefaction and thinning of the collagenous fibers with predominance of the elastic tissue in the corium, and a marked diminution of subcutaneous

fat. With very slight trauma, the epidermis splits and gapes. The skin shows a whorled disorderly structure; the collagen bundles of fibrils seem to have insufficiently united into collagen fibers and fiber-bundles (Fig. 9). The numerous fissures show loose connection of structures in the stratum reticulare with the epidermis and underlying muscle and bone. The scarring is apparently due to an abnormal regeneration of connective tissue which is even looser than the original tissue in structure. Apparently fibroblastic proliferation is decreased.

The spheroids or small cyst-like tumors found in the subcutaneous tissue feel like freely movable peas. They are formed from subcutaneous fat and by gradual thinning and atrophy become free bodies in the loose subcutaneous tissue. In time they become oil-containing cysts with thickened, fibrous, even calcareous walls.



NORMAL COLLAGEN

COLLAGEN IN THE EHLERS-DANLOS SYNDROME (after Jansen, L. H.)

Fig. 9.—Collagen in normal subjects and in patients with the Ehlers-Danlos syndrome.

There is no tendency to excessive hemorrhage from wounds or when a tooth is extracted, and there is no abnormality regarding blood cell counts, bleeding time, or coagulation time. Some of the bruises and slight hematomata in the Ehlers-Danlos syndrome have been confused with "blood blisters" and with elevation of the epidermis from the dermis which are characteristic of dystrophic types of epidermolysis bullosa.[22] Samuels, Schwartz, and Meister suggest that defective elastic tissue along with a diminution in collagen may be primarily responsible for the increased capillary fragility. That elastic fibers play an important role in capillary fragility has been demonstrated in histologic study of petechiae produced by negative pressure in normal persons. Apparently fragmentation of the elastic tissue occurs with no damage to the endothelium of the blood vessels; the erythrocytes escape by diapedesis.[23]

Most authorities consider that the laxity of the skin and joints is due to an abnormal increase in the elastic tissue of the corium, which is arranged in irregular and coarse bundles. The recent work by Jansen with electron microscopy points toward a defect in the collagen fibril-bundles in the dermis, hypodermis, and joints as the most likely explanation for the symptoms of this condition. The abnormal structure of the collagen may be present in different degrees and may be confined to various tissues of the body and in different regions. The etiology remains obscure, but the condition is apparently hereditary. Husebye demonstrated the syndrome in four generations,[24] and Johnson and Falls, in six generations.[12] In both families the syndrome was inherited as a Mendelian dominant. There are marked tendencies for skeletal anomalies and other deformities to occur simultaneously. The condition apparently does not affect longevity.

TREATMENT

There is no specific treatment for this syndrome other than prompt recognition and prevention of undue trauma. Lacerations, which usually occur as a result of unstable joints which allow stumbling and falling, are most successfully treated by approximating the edges with adhesive. Sutures may tear out easily. Orthopedic appliances and operations may be necessary in the treatment of extreme articular laxity. Associated anomalies should be treated appropriately

when discovered. The most important aspect of therapy should be directed toward stabilization of the joints and toward prevention of injury to the fragile skin and blood vessels. Some authors advise high-fat diets in order to induce increased fat deposition in the subcutaneous tissue. With the passing years and increased fat depots, the need for precautionary measures decreases as the hypodermis becomes a much better buffer for trauma.

SUMMARY

The Ehlers-Danlos syndrome is a hereditary symptom complex consisting of fragility of the skin and blood vessels and extreme laxity of the skin and joints. Other common features are the papyraceous scars and pseudotumors of the subcutaneous tissue. A case with these features is reported exhibiting a large subgaleal hematoma and left facial palsy. The literature is reviewed regarding etiology and pathology, and explanations are offered for the symptoms and signs of the syndrome.

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Muscular Dystrophy

V. Blood Sugar and Serum Electrolytes Following Insulin and Dextrose, Alone or in Combination

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It has been adequately demonstrated that the patient with muscular dystrophy can readily dispose of carbohydrate loads * and that the response to insulin, as reflected in capillary blood sugar levels, is somewhat less than in healthy children.[6] The fact that in muscular dystrophy the muscles which form the bulk of the body tissues in which glucose may be utilized are diseased suggests that the effective disposal of such carbohydrate loads is achieved by a greater reliance upon pathways other than those in muscle. This is evident in the electrolyte changes herein reported following acceleration of carbohydrate metabolism by glucose, insulin, or insulin and glucose in children with muscular dystrophy.

MATERIALS AND METHODS

Healthy boys and girls in a well-run home for children and children with a diagnosis of the juvenile form of muscular dystrophy were given crystalline insulin,† 0.1 units per kilogram of body weight, and dextrose, 0.5 gm. per kilogram as a 50% solution in water, intravenously, alone or in combination. Possible adverse effects of carbohydrate restriction ‡ were avoided by provision of a full diet for several days prior to the tests. The injections were made in three to five minutes, following a night of fasting and of bed rest. Samples of venous blood were withdrawn with minimal stasis for blood sugar and serum electrolyte analyses prior to and at one-half hour intervals thereafter during continued bed rest. The analytic procedures for blood sugar and serum inorganic phosphorus, potassium, total CO_2 content expressed as bicarbonate, chloride, and sodium were those in regular use in this laboratory.[10]

RESULTS

A. Intravenous Insulin.—In healthy children the administration of crystalline insulin, 0.1 units per kilogram of body weight, lowered the level of sugar in the blood and produced a distinct decrease in the serum inorganic phosphorus, potassium, and bicarbonate and a definite rise in chloride. The changes in phosphorus and in potassium following insulin have been described previously,§ whereas the bicarbonate and chloride alterations have only become evident in the course of our control studies. The same procedure in the patients with muscular dystrophy produced a comparable fall in blood sugar at the 30-minute point, but this was accompanied by much less of a decrease in serum inorganic phosphorus, potassium, and bicarbonate. The rise in chloride was about the same in the two groups of subjects. These changes are summarized in Figure 1.

B. Intravenous Dextrose.—The rapid injection of dextrose, 0.5 gm. per kilogram as a 50% solution in water, produced comparable increments in the concentrations of blood sugar in both groups of children (Fig. 2). The fall in serum inorganic phosphorus

Submitted for publication Aug. 31, 1955.

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Established Investigator of American Heart Association (Dr. Mateer).

* References 1-6.

† Obtained from the hospital pharmacy and therefore containing 5% to 10% of the hyperglycemic-glycogenolytic factor.[7]

‡ References 7-9.

§ References 11-16.

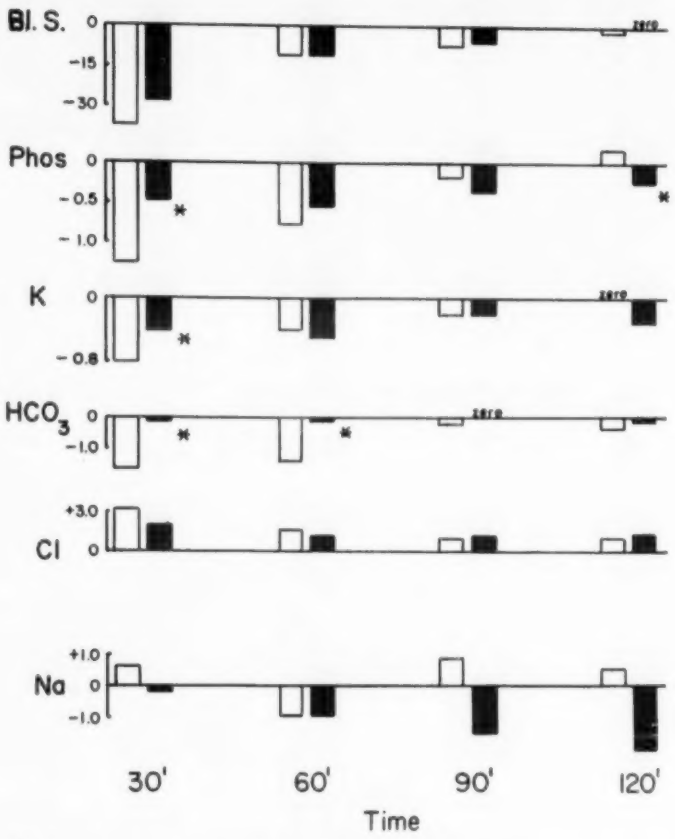

Fig. 1.—Venous blood sugar and serum electrolyte levels following intravenous crystalline insulin (0.1 unit/kilogram). Though the blood sugar decrease following insulin administration to 12 children with muscular dystrophy was 28 mg. per 100 cc. (solid columns), in contrast to 37 mg. per 100 cc. in 10 normal children (open columns), this difference is not statistically significant. On the other hand, the smaller changes in serum inorganic phosphorus, potassium, and bicarbonate are significant.

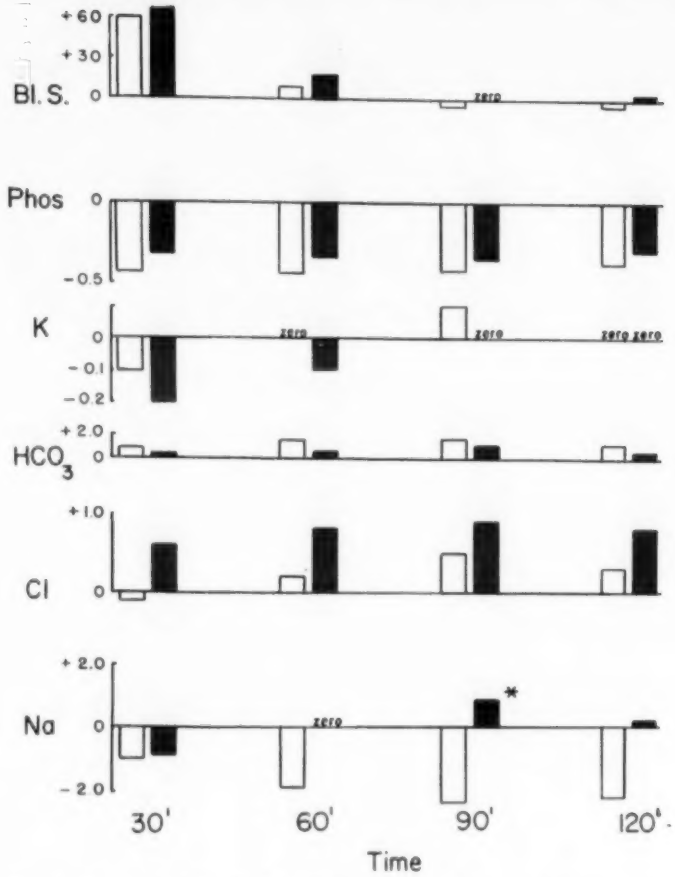

Fig. 2.—Effects of intravenous dextrose (0.5 gm/kilogram) in venous blood sugar and serum solutes. It is readily evident that the hyperglycemia and the fall in serum inorganic phosphorus was of the same order of magnitude in 27 normal boys and girls (open columns) and 23 children with muscular dystrophy (solid columns). The difference in the phosphorus response in the two groups is close to statistical significance, however, in that P was 0.06. All other changes, except for the 90-minute sodium, were also of the same order of magnitude in these two groups of children.

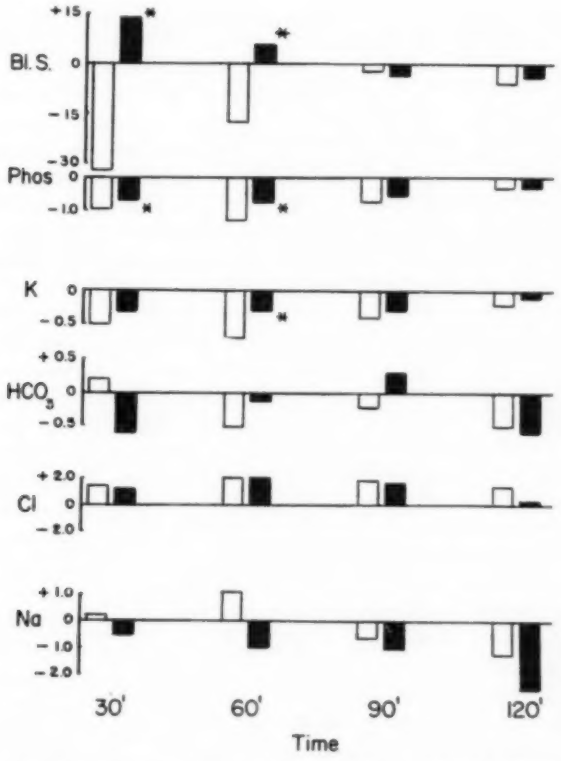

Fig. 3.—Venous blood sugar and serum electrolyte changes following intravenous dextrose (0.5 gm/kilogram) and insulin (0.1 unit/kilogram). In 10 children with muscular dystrophy (solid columns) the administration of dextrose and insulin produced an average increase of 14 mg. per 100 cc. in the blood sugar at 30 minutes, in contrast to the 32 mg. per 100 cc. drop in 11 healthy children (open columns). The difference was still evident at 60 minutes. Serum inorganic phosphorus decreased to a smaller degree at 30 and 60 minutes in children with muscular dystrophy and this was also true of the fall in serum potassium at 60 minutes.

known to follow dextrose administration || was of equal or almost equal degree in the normals and in the children with dystrophy. As a preliminary to the later discussion of the findings of Van Bekkum and Querido, it is to be noted that the somewhat smaller drop in serum phosphorus in the latter group at the 30-minute point is close to being statistically significant, with a *P*-value of 0.06. The net changes in the other electrolytes, i. e., in potassium, bicarbonate, sodium, and chloride, if present were of the same order of magnitude in both groups. These data are all shown in Figure 2.

|| References 17-27.

C. Intravenous Dextrose and Insulin.—The combination of insulin and dextrose resulted in a rise in the 30- and 60-minute blood sugar levels in the children with muscular dystrophy in contrast to the decrease recorded in our control studies (Fig. 3) and in those of others.[28] In both groups the drop in serum inorganic phosphorus and in potassium noted with insulin alone is again seen; again, as with insulin alone, the decrement in these two serum electrolytes is less in the children with muscular dystrophy (30- and 60-minute points in the case of phosphorus and 60-minute sample in the case of potassium). Bicarbonate,

chloride, and sodium changes were the same in the two groups.

COMMENT

A. Responses to Insulin.—The administration of insulin to a fasting subject accelerates carbohydrate disposal and lowers the blood sugar level by deposition of glucose as tissue and especially as muscle glycogen and by utilization of glucose within tissues.[29] In previous studies with muscular dystrophy,[6] we have noted a capillary blood sugar decrease following intravenous insulin which is less than that elicited in healthy children. In the work herein reported in which venous blood sugar levels were measured no differences were detectable. This suggests that capillary blood is a more sensitive indicator of the abstraction of glucose by tissues, perhaps because it mirrors the net removal of glucose by muscle more accurately than does the venous drainage from all of the tissues of the arm on which the venipuncture is performed. The electrolyte changes accompanying these processes indicate, however, that carbohydrate disposal is indeed altered in muscular dystrophy, even though the blood-sugar responses may be the same as those in normals or only slightly different. In the normal subjects distinct decreases in phosphorus and in potassium accompany the drop in blood sugar following the administration of insulin. Both of these changes can be taken to reflect disposal of carbohydrate either via the formation of tissue glycogen or via glycolysis within cells. Both processes are known to abstract these particular electrolytes from surrounding media.¶ The participation of the liver as a factor in these events can be excluded because hepatic glycogenolysis and gluconeogenesis from protein, accelerated by insulin in the absence of carbohydrate loading, are known to release rather than abstract potassium and phosphorus. Hence, the finding of a smaller change in serum inorganic phosphorus and in potassium in muscular dystrophy following insulin clearly indicates either decreased tissue glycolysis, decreased glycogenation of extrahepatic tissues, or both.

Further support for the above interpretation is present in the serum chloride and bicarbonate data following insulin administration to these two groups of children. In the normal group the serum chloride almost always shows a definite rise accompanied by a distinct fall in the bicarbonate level. It is as if the entrance of phosphorus and of potassium into the cell ultimately resulted in a transfer of cell chloride to the extracellular fluids, with a subsequent decrease in bicarbonate. In muscular dystrophy these transfers, whatever their origins, are quantitatively less. Hence, the concurrence of these changes with the smaller decreases in potassium and phosphorus again is compatible with the presence of inadequate tissue glycolysis and glycogenation in muscle. This could result either from a reduction in the absolute muscle mass or reflect a functional deficiency of diseased muscles.

Why then, is the diminished disposal of carbohydrate not reflected more clearly in the levels of blood sugar? One reasonable possibility is that homeostasis is maintained by the liver, which releases less glycogen or reduces gluconeogenesis in response to decreased extrahepatic disposal.[29] The fact that liver function is normal in these patients in all other respects in which we have tested it justifies such a view.[34]

B. Responses to Intravenous Dextrose.—In the healthy children the injection of dextrose in these amounts raised the blood sugar above the fasting levels and produced the decrease in serum inorganic phosphorus referred to earlier. This reflects in greater part the removal of extracellular inorganic phosphorus for the phosphorylation of glucose and its derivatives during glycolysis in cells and, to a smaller extent, the segregation of glucose as liver glycogen. Both of these processes are known to pre-empt extracellular phosphorus, though the former does so to a much greater degree.# The tendency for the serum total CO_2 content to increase

¶ References 30-33.

References 30 and 33.

may merely reflect a shift in the metabolic mixture from a fat to a carbohydrate substrate; this in turn would decrease the undetermined acids in serum allowing the total CO_2 content to rise.

The fact that the muscular dystrophic child has comparable blood sugar responses even though his muscle mass is reduced or defective merely indicates that administered glucose can be disposed of by pathways that do not pre-empt electrolytes to the same degree, i. e., transformation to fat or protein, or glycogenation in tissues other than muscles.

We have been unable to duplicate in children the finding of Van Bekkum and Querido in adults [35] that the mean serum inorganic phosphorus change following intravenous dextrose is less in muscular dystrophic than in healthy subjects. As pointed out earlier, in our series comparison of the changes in serum inorganic phosphorus seen in 23 children with muscular dystrophy with those in 27 healthy boys and girls yields a *P*-value for the *t*-test of 0.6. Basing the comparison on the maximal phosphorus decrease, as was done by Van Bekkum and Querido, or limiting it to the more seriously involved children still fails, however, to demonstrate a statistically significant difference.

C. Effects of Glucose and Insulin.—The data in Figure 3 suggest that this combination presents a load of dextrose, exogenous and perhaps endogenous, which proves excessive in the muscular dystrophic subjects compared to the healthy children. The smaller decreases in serum inorganic phosphorus and in potassium are compatible with this view. An explanation based on defective liver glycogenation is untenable, since our patients had no evidences of liver disorder and since in patients with cirrhosis or other liver diseases with diminished hepatic glycogenesis the decrease in serum inorganic phosphorus is greater than in normals * and contrasts with the smaller change recorded in our subjects with muscular dystrophy.

* References 36-44.

It should again be pointed out that the studies with insulin were all conducted prior to the ready availability of glucagon-free preparations of this hormone.

SUMMARY AND CONCLUSION

Though children with muscular dystrophy responded to intravenous insulin with venous blood sugar changes that were indistinguishable from normal, there was definite evidence of altered carbohydrate disposal in that the characteristic decreases in serum inorganic phosphorus, potassium, and bicarbonate which follow insulin administration were of distinctly smaller magnitude.

The injection of dextrose intravenously produced comparable rises and subsequent falls in the levels of blood sugar in the dystrophic and in the control group. The smaller decrement in serum inorganic phosphorus reported by other workers in a limited number of patients with this disease was not evident in our larger group of children.

Insulin and dextrose in combination produced hyperglycemia in muscular dystrophy and hypoglycemia in control subjects. This inadequate disposal of glucose from exogenous and perhaps endogenous sources is compatible with decreased extrahepatic utilization as a result of diseased musculature with resultant smaller changes in serum inorganic phosphorus and potassium. An alternative explanation that the hyperglycemia is attributable to inadequate deposition of glucose as liver glycogen in the presence of insulin and carbohydrate seems unlikely in view of the well-documented demonstration that in liver disease the phosphorus decrease is exaggerated rather than diminished as it is in the dystrophics.

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Muscular Dystrophy

VI. Diminished Blood Sugar and Serum Electrolyte Responses to Epinephrine

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In recent studies in this and in other laboratories it has been shown that even though glucose tolerance tests are normal in muscular dystrophy the serum electrolyte responses to acceleration of carbohydrate metabolism often differ from these seen in normal subjects. Thus, Van Bekkum and Querido have reported that the administration of dextrose produced a smaller decrease in the serum inorganic phosphorus of adult patients in the far-advanced stage of muscular dystrophy.[1] This was not evident in our series of children with early and late forms of the disorder.[2] However, the administration of insulin to members of this same group produced less of a drop in serum inorganic phosphorus, serum potassium, and serum bicarbonate; this was also true when insulin and dextrose were administered in combination.[2] In the studies with dextrose or with insulin alone the venous blood-sugar responses were within the range observed in control subjects under the same conditions; in the insulin-dextrose studies the patients with muscular dystrophy developed hyperglycemia, whereas the healthy children showed hypoglycemia.*

It has been recognized that the administration of epinephrine ultimately produces a decrease in the concentrations of serum potassium† and serum inorganic phosphorus,‡ in addition to a rise in the blood sugar. These findings are not in conflict with the organ perfusion studies nor the serum measurements in which a transient increase or decrease-increase in serum potassium has been noted immediately after epinephrine administration.§ In this paper the blood sugar and serum electrolyte responses following the subcutaneous administration of epinephrine to healthy subjects and to patients with muscular dystrophy are defined.

MATERIAL AND METHODS

A 1:1000 aqueous solution of epinephrine (free of arterenol [norepinephrine]) was injected subcutaneously into healthy subjects and into patients with muscular dystrophy. Following an overnight fast, a total of 0.01 ml. per kilogram of body weight was administered in divided dosage at 0, 10, and 20 minutes. Occasional patients complained of palpitation, and flushing was noted. Intervening measurements of pulse rate and blood pressure showed either no change or a slight rise with about equal frequency in the muscular dystrophy and the control groups. Samples of venous blood for blood sugar and serum electrolyte analyses were obtained with minimal stasis at 0, 30, 60, 90, and 120 minutes.

RESULTS

The blood sugar changes presented in Figure 1 show less of a hyperglycemic response in patients with muscular dystrophy. The differences in the rises present in the two groups at 60, 90, and 120 minutes are statistically significant. Similarly, a smaller

Submitted for publication Aug. 31, 1955.

From the Department of Research Medicine and the Children's Hospital, University of Pittsburgh School of Medicine.

Aided by grants from the Muscular Dystrophy Association of America, Incorporated.

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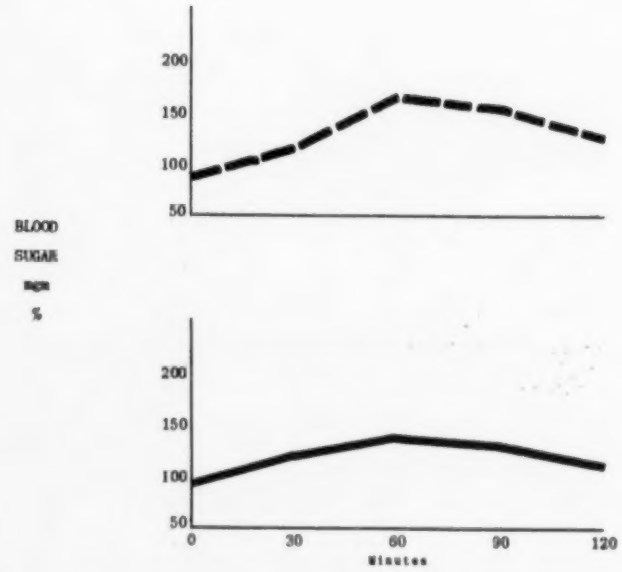
* References 2 and 3.

† References 4-6.

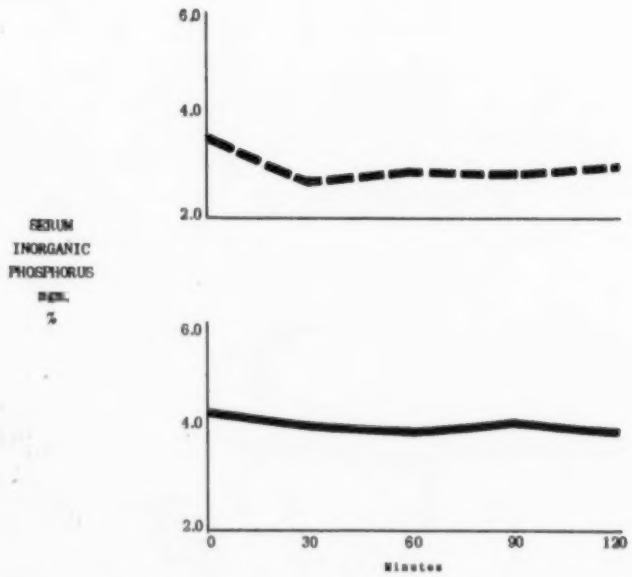
‡ References 7 and 8.

§ References 9-13.



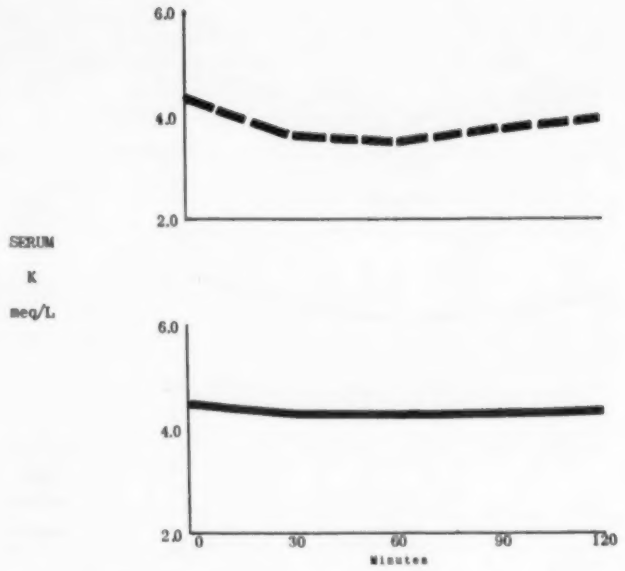
MEAN ± S.D.	HEALTHY	+37.7 ± 14	+72.1 ± 21	+66.4 ± 23	+39.5 ± 24
	MUSCULAR DYSTROPHY	+30.2 ± 18	+48.3 ± 26	+40.9 ± 26	+21.0 ± 16
	"p"	0.25	0.02*	0.017*	0.027*

Fig. 1.—Blood sugar concentrations following subcutaneous epinephrine. Epinephrine in comparable amounts produced less hyperglycemia in 15 patients with muscular dystrophy (solid line) than in 11 control subjects (broken line).



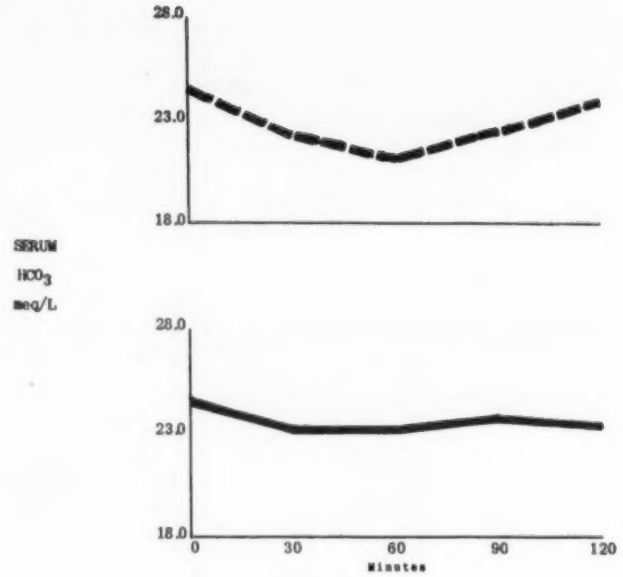
Mean ± S.D.	HEALTHY	−0.84 ± 0.3	−0.87 ± 0.3	−0.70 ± 0.4	−0.62 ± 0.4
	MUSCULAR DYSTROPHY	−0.28 ± 0.2	−0.33 ± 0.3	−0.25 ± 0.2	−0.33 ± 0.3
	"p"	<0.0001*	<0.0001*	<0.0003*	<0.03*

Fig. 2.—Serum inorganic phosphorus changes following epinephrine. Epinephrine administration was followed by a smaller decrease in serum inorganic phosphorus in the patient with muscular dystrophy (solid line) than in the control subjects (broken line).



Mean ± S.D.					
	HEALTHY	−0.71 ± 0.4	−0.91 ± 0.4	−0.69 ± 0.4	−0.43 ± 0.2
	MUSCULAR DYSTROPHY	−0.16 ± 0.4	−0.18 ± 0.5	−0.15 ± 0.4	−0.07 ± 0.4
	"p"	0.0013*	0.0005*	0.0015*	0.015*

Fig. 3.—Serum potassium changes following epinephrine. In muscular dystrophy the serum K change following epinephrine is distinctly less than in control subjects.



Mean ± S.D.					
	HEALTHY	−2.3 ± 1.1	−3.6 ± 1.2	−2.3 ± 1.1	−0.9 ± 1.0
	MUSCULAR DYSTROPHY	−1.4 ± 1.5	−1.4 ± 1.4	−1.3 ± 1.8	−1.4 ± 2.0
	"p"	0.12	0.0006*	0.12	0.52

Fig. 4.—Serum bicarbonate levels after epinephrine. At the 60-minute point the control subjects (broken line) showed a greater decrease in serum total CO_2 content expressed as bicarbonate than did the patient with muscular dystrophy.

decrease in the serum inorganic phosphorus and in the serum potassium was observed throughout in the muscular dystrophy patients (Figs. 2 and 3). The P for the t-test ranged from 0.03 to less than 0.0001.

In the cases of the serum total CO_2 content, the muscular dystrophy patients manifested a smaller decrease, which was statistically significant only at the 60-minute point (Fig. 4). There were no differences in the responses in serum sodium or chloride, and hence graphic presentation of these has been omitted.

COMMENT

In 1933, Elkington and Goldblatt[14] reported that in three cases of muscular dystrophy the hyperglycemia which followed upon epinephrine administration was less than that seen in six control subjects. The validity of this observation might be questioned in that the fasting levels in the muscular dystrophy patients were distinctly higher than in the normal subjects. Our studies establish, however, that the muscular dystrophic on the average does respond with less of a hyperglycemia following the administration of epinephrine, as shown when it was given in equivalent dosage to healthy subjects and to patients afflicted with this disease.

Epinephrine is believed to raise the blood sugar level by altering liver phosphorylase activity, with resultant glycogenolysis,‖ and by blocking the assimilation or utilization of glucose in the tissues.¶ It may also be that epinephrine increases gluconeogenesis and thereby contributes to the hyperglycemia.

In view of the first of these possibilities, and assuming comparable absorption of epinephrine, the lower blood sugar response to epinephrine in the muscular dystrophy group might be attributed to decreased release of liver glycogen. This could represent (*a*) decreased activation of liver phosphorylase by epinephrine, or point to either (*b*) tenaciously held normal stores of liver glycogen or (*c*) depletion of liver glycogen. The normal blood sugar responses to insulin cited earlier[2] argue against, but do not exclude, any of these possibilities. There is furthermore no evidence of liver disease in routine hepatic indices (serum bilirubin, alkaline phosphatase, prothrombin, cephalin flocculation, thymol turbidity, albumin, globulin, cholesterol, and B. S. P. excretion.[19] This does not exclude, of course, other anomalies of liver function, enzymatic or otherwise, not reflected in these indices. However, another explanation that does take into account the muscle defect in this disease can be offered. This necessitates a modification of our current views of the contribution of glycogenolysis to epinephrine hyperglycemia. These observations of a decreased epinephrine hyperglycemia in muscular dystrophy suggest the possibility that the blood sugar rise following epinephrine comes in part from hepatic deglycogenation and in part from muscle deglycogenation, with conversion of the resultant lactic acid to liver glycogen and blood sugar. This glycogenolytic effect of epinephrine varies from muscle to muscle but is well established.[20] Since muscle defects and abnormalities of muscle glycogen are present in muscular dystrophy,[21] these could account for the decreased blood sugar response. The smaller electrolyte changes can then be attributed to decreased utilization of glucose in muscle with less of the drop in the serum inorganic phosphorus and in potassium associated with glycolysis. The changes in the serum bicarbonate would in both cases represent an accumulation of anionic metabolites or undetermined acids in the course of carbohydrate utilization. As this fraction rises there occurs a proportionate fall in the serum total CO_2 content.

The second of the two possibilities raised earlier, i. e., that the smaller degree of hyperglycemia in muscular dystrophy results from a decrease in the usual epinephrine blockade of glucose assimilation or utilization by the tissues, appears to be unlikely in view of the concomitant electrolyte changes cited above. One would expect that if the

‖ References 15 and 16.

¶ References 17 and 18.

disease process did facilitate the peripheral disposal of glucose, the accompanying changes in serum inorganic phosphorus, potassium, and bicarbonate would be of greater rather than smaller magnitude.

Our data provide no answer to the third possibility, that part of the epinephrine induced hyperglycemia represents increased gluconeogenesis and that muscular dystrophy diminishes this contribution.

SUMMARY AND CONCLUSIONS

Epinephrine injected subcutaneously into patients with muscular dystrophy produces a smaller degree of hyperglycemia than that observed in control subjects. This may reflect a lower phosphorylase response, tenacious hepatic glycogen stores unresponsive to phosphorylase, or diminished amounts of liver glycogen. Another possibility is suggested: In contrast to current views, our data are compatible with but do not establish the possibility that epinephrine hyperglycemia originates in part from a release of liver glycogen and in part from a conversion of muscle glycogen to lactic acid, liver glycogen, and ultimately blood sugar. Functionally defective or decreased stores of muscle glycogen could then account for less epinephrine hyperglycemia in muscular dystrophy. The smaller decrease in serum inorganic phosphorus, in potassium, and in serum total CO_2 content in muscular dystrophy are all compatible with a smaller carbohydrate load and a lower degree of acceleration in carbohydrate metabolism following epinephrine.

The lower electrolyte changes cited above argue against the second possibility, that in muscular dystrophy the usual epinephrine blockade of glucose assimilation or disposal in peripheral tissues is diminished, thereby accounting for the lower degree of hyperglycemia.

Our findings do not exclude the possibility that in muscular dystrophy there is a decreased contribution from gluconeogenesis to the epinephrine hyperglycemia.

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Muscular Dystrophy

VII. Trials of a Pituitary Growth Factor

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The demonstrations that pituitary growth hormone increased muscle and organ size and induced the retention of nitrogen and of electrolytes * prompted trials of this factor in muscular dystrophy when a "nondiabetogenic" preparation became available.

MATERIAL AND METHODS

Four children, 4 to 7 years of age, believed to have muscular dystrophy on the basis of clinical findings, biopsy of muscles, and laboratory studies, which have been described in greater detail in earlier publications,† received a preparation of pituitary growth factor for six to eight months at a daily dosage level of 3.0 mg. I. M. per kilogram of body weight. This material was prepared in accordance with the procedure of Raben and Westermeyer [20] and found to restore growth in immature hypophysectomized mice.‡ The following observations were made in each of the four children:

A. Muscle strength was evaluated by the physical therapist prior to, during, and after the course of growth factor.

B. Blood was withdrawn at intervals before breakfast for measurment of sugar and N. P. N. concentrations, as well as for serum CO_2, chloride, sodium, potassium, phosphorus, calcium, cholesterol, and albumin levels.§

C. In two of the subjects electrolyte and nitrogen balance studies were conducted prior to and shortly after the start of growth factor therapy.

D. Evidences of diabetogenic, thyroid-stimulating, adrenocorticotropic, gonadotropic, or melanophore factors in the medication were sought by determinations of insulin or glucose tolerances,‖ levels of protein-bound iodine,[23] blood eosinophile counts,[24] urinary 17-ketosteroid excretion rates,[25] bioassays for ovarian-uterine-stimulating properties of urine colloids in immature mice,[26] and photography and biopsy of new pigment spots, respectively.

E. In view of the finding that in animals growth factor has produced alterations in blood volume and in blood clotting time,[27] serial measurements of the blood cells, hematocrit, sedimentation rate, red cell fragility, bleeding, clotting and clot retraction, prothrombin level, cephalin flocculation, alkaline phosphatase, thymol turbidity, and bilirubin were obtained.

RESULTS

Approximately 600 injections of the growth-factor preparation were given without a single local reaction. This was true even in resumption of treatment after interruptions lasting one to eight days.

A. From Table I it is readily evident that serial measurements of muscle strength showed no improvement during therapy with growth factor, nor was there any sudden deterioration following withdrawal of the medication.

B. There was no evidence that the growth factor induced any pattern of change in the blood and serum solutes (Table II). In particular it should be noted that the fasting venous blood sugar levels did not rise, nor were serum proteins changed. The already high serum inorganic phosphorus levels, re-

Submitted for publication Aug. 31, 1955.

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Supported by grants-in-aid from the Muscular Dystrophy Associations of America, Incorporated, the United States Public Health Service, and the American Urologic Research Foundation.

* References 1-15.

† References 16-19.

‡ Prepared, tested, and supplied through the kindness of Dr. Gustav Martin, of the National Drug Company; see Appendix for bioassay.

§ References 21 and 22.

‖ Reference 18. Danowski, T. S.: Unpublished data.

Table I

MUSCLE STRENGTH IN RELATION TO GROWTH FACTOR THERAPY

Patient	Date	Treatment	MUSCLE STATUS									
			Trunk R.	Trunk L.	Abdominals R.	Abdominals L.	Lower extremities R.	Lower extremities L.	Neck R.	Neck L.	Upper extremities R.	Upper extremities L.
J.B.	7/3/52	none	3	8	30	30	32	33	30	30	34	37
	1/8/53	none	3	8	30	30	33	35	30	30	35	37
	7/24/53	growth hormone										
	10/7/53	growth hormone	18	18	20	30	29	32	25	25	30	30
	1/21/54	none	18	18	20	20	28	27	25	25	34	35
J.C.	11/10/52	none	60	60	35	35	40	40	45	45	61	59
	7/8/53	none	65	65	35	35	51	51	45	50		
	7/23/53	growth hormone										
	10/20/53	growth hormone	75	75	25	25	41	41	60	60	66	66
	12/22/53	growth hormone	65	60	28	28	52	53	60	60	70	73
	1/23/54	none	60	60	25	25	48	49	60	60	72	70
P.D.	3/12/53	none	25	25	40	40	42	42	15	15	51	53
	7/31/53	growth hormone										
	10/9/53	growth hormone	50	50	37	37	45	46	28	28	57	60
	12/17/53	growth hormone	75	60	35	35	50	48	20	15	60	56
	1/29/54	none	75	75	35	35	50	53	15	13	61	62
J.M.	4/29/53	none	60	60	40	40	62	62	45	45	70	66
	5/1/53	growth hormone										
	10/10/53	growth hormone	60	60	60	60	52	54	55	55	70	60
	4/6/54	none	60	60	60	60	61	59	55	60	60	70

Graded in accordance with the following table:
N or 100% = NORMAL = function against gravity and normal resistance
G or 75% = GOOD = function against gravity and some resistance
F or 50% = FAIR = function against gravity only
P or 25% = POOR = function in horizontal plane
T or 10% = TRACE = a few fibers have active function
Intermediate grades, i.e., F' or F" represents an estimated 10 per cent lesser or greater function

Table II

SERUM AND BLOOD CONSTITUENTS IN MUSCULAR DYSTROPHY PATIENTS RECEIVING GROWTH FACTOR

Patient	Date	Treatment	Blood Sugar mg%	NPN mg%	HCO_3 mEq/l	Cl mEq/l	Na mEq/l	K mEq/l	Alb. gm%	Glob. gm%	Ca mg%	Phos. mg%	Chol. mg%
J.B.	7/17	none	47	39	13.3	100.4	140	4.2			11.0	5.72	332
	7/24	growth hormone											
	8/19	" "	106	30	19.7	100.0	146	4.4				5.39	223
	10/19	" "					146	4.4	4.64	2.31			230
	12/3	" "	95	36	17.0	104.6	143	4.4	4.11	2.73	10.0	5.53	138
J.C.	11/1	none	72	27	21.8	97.6	145	3.6	4.30	2.26	10.6	5.53	200
	11/5	"										5.94	
	7/14	"	95	25	21.3	103.5	144	4.4	4.54	2.70	10.2	6.24	241
	7/18	"	102	47	21.8	100.1	148	4.6			10.4	5.24	234
	7/31	"	108	27	21.0	104.7	146	4.4	3.95	3.75		4.67	229
	7/25	growth hormone											
	9/24	" "			20.9	97.3	146	4.3	5.21	2.91	10.3	4.91	241
	11/19	" "	102	34	21.7	99.3	143	4.5	5.06	2.62	12.0	5.67	
P.D.	3/9	none	72	31	21.3	99.8	142	4.4	3.30	2.72	10.3	5.02	172
	4/21	"	87	32	18.4	104.9	148	4.7	4.22	2.88	10.8	5.50	162
	4/22	"	72	33	19.6	102.5	144	5.4	3.85	2.86	9.8	6.02	147
	4/27	"	86	40	21.2	102.2	143	4.6	3.90	2.70	9.8	5.89	186
	4/29	"	88	33	22.4	100.6	145	4.8	4.30	2.42	10.1	6.02	190
	5/3	"	91	34	21.5	98.2	143	4.6	3.97	2.54	10.1	5.63	150
	5/6	"	113	36	23.5	99.1	138	4.7	4.49	3.14	10.6	5.39	231
	7/31	growth hormone											
	8/31	" "			20.5	96.6	144	4.4	4.21	2.99	10.3	5.49	151
	9/16	" "			20.2	98.1	146	4.5	4.36	3.18	10.0	6.28	225
	9/21-24	" "	87	28								5.23	206
	10/8	" "										5.49	205
	12/3	" "			21.3	102.1	141	4.4	4.89	2.32	9.8	5.22	186
J.M.	4/16	none	87	40	22.5	99.2	148	4.2	4.67	2.93	10.6	5.24 5.77	231
	4/21	"											
	5/1	growth hormone											
	5/9	" "	91	30	24.4	97.9	142	4.6	3.72	3.22	9.8	4.78	224
	5/12	" "	86	30	22.9	97.9	140	4.0	4.54	2.88	9.8	4.75	225
	5/15	" "	90	40	21.8	101.3	140	3.7	4.26	2.74	10.5	4.62	253
	5/18	" "	91	39	23.3	98.2	146	4.2	4.10	3.01	9.8	4.71	206
	5/22	" "	80	35	22.5	96.8	138	4.8	4.12	3.10	10.4	4.37	200
	5/25	" "	106	36	22.7	100.2	141	4.4	4.17	3.11	9.8	4.78	200
	6/21	" "	91	31	20.1	102.7	146	3.8	3.72	3.25		4.63	
	9/16	" "			22.5	99.2	145	4.2	4.78	2.86	10.6	5.24	
	9/21-24	" "	88	33	22.2	104.7	144	4.8	4.13	2.67	9.8	5.49	425
	11/16	" "	102	32	22.9	104.1	144	4.3	4.47	2.89	10.2	4.97	286

Table III

WATER, NITROGEN, AND ELECTROLYTE BALANCES WITH AND WITHOUT GROWTH HORMONE THERAPY

Patient and Period	Days	Growth Hormone (mgm/d)	EXTERNAL BALANCE				
			H_2O* (L)	Cl (mEq)	Na (mEq)	K (mEq)	TN (gm)
P.D. 4/24 4/27	3	none	+0.7	+78	+ 65	+ 94	+25.6
4/27 4/30	3	none	-0.4	+32	+ 27	+ 34	+ 9.4
4/30 5/3	3	75	-0.2	+58	+ 30	+ 37	+ 9.8
5/3 5/6	3	75	-0.7	+29	+ 26	+ 12	+ 3.8
J.M. 5/9 5/12	3	60.6		+19	+ 6	+ 41	+18.96
5/12 5/15	3	60.6		+28	+ 23	+ 32	+ 6.32
5/15 5/18	3	60.6		+80	+ 68	+ 82	+18.77
5/18 5/22	4	60.6		+28	+134	+127	+22.88
5/22 5/25	3	none		-13	- 10	- 33	- 1.38

*Based on changes in body weight converted for solids ingested and excreted

ported in an earlier publication as frequently present in muscular dystrophy,[18] were not discernibly altered. The fluctuations in the values were within the range observed to occur spontaneously in healthy children.¶

C. The balance data (Table III) covering intervals prior to and during growth-factor therapy revealed only minor changes in the retention of potassium, sodium, and chloride, without distinct alteration in the balance of nitrogen.

D. There was no evidence upon comparison with healthy controls or with the patient's pretreatment responses that the therapy

¶ Danowski, T. S.: Unpublished data.

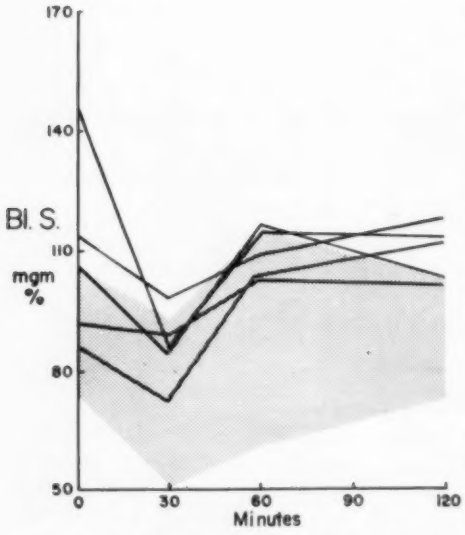

Fig. 1.—Insulin tolerance studies during growth-factor therapy. The solid background indicates the response to insulin, 0.1 unit per kilogram of body weight, in a group of 15 children with muscular dystrophy, mean ± 1 S. D.[18] The solid lines indicate that responses of children with muscular dystrophy while on growth factor are not clearly different from the control observations.

clearly altered insulin or glucose tolerances (Figs. 1-3). Similarly, the protein-bound iodine levels which in many clinical conditions accurately reflect the level of thyroid function showed no change (Table IV). This was true in the early phase of treatment, to which thyroid-stimulating-hormone effects are usually confined, as well as later. With one exception, the urinary output of 17-ketosteroids showed none of the pronounced rise which follows adrenocortical discharge by corticotropin (ACTH) (Table V). Some slight increases did occur in the first three patients. In J. M., however, a distinct increase in the output of 17-ketosteroids was recorded toward the end of therapy. Eosinophile levels were never found depressed when measured in the fasting state during the treatment phase. If gonadotropins were present in the current preparation, they did not appear in the urine (Table VI). Clinical observations and photography indicated that within several days of the start of treatment collections of dark brown pigment appeared on the face of all four patients. As treatment continued, usually no further pigmentation developed. Biopsy of tissue from J. M. showed pigmented junctional nevi without evidence of malignancy.

E. Serial measurements of hematocrit, sedimentation rate, red blood cell fragility, bleeding, clotting, and clot retraction time,

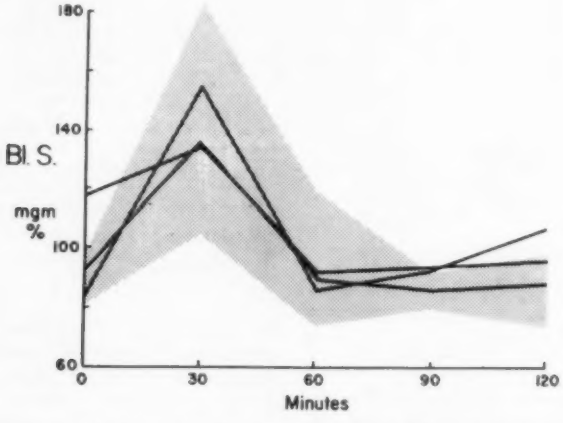

Fig. 2.—Intravenous dextrose tolerance response in children with muscular dystrophy receiving growth factor. The blood sugar responses of 10 children with muscular dystrophy prior to any therapy are indicated by the dotted background figure representing the mean values ± 1 S. D. It is evident that the responses of the three children with muscular dystrophy receiving growth factor as indicated by the solid lines showed no impairment of carbohydrate disposal.

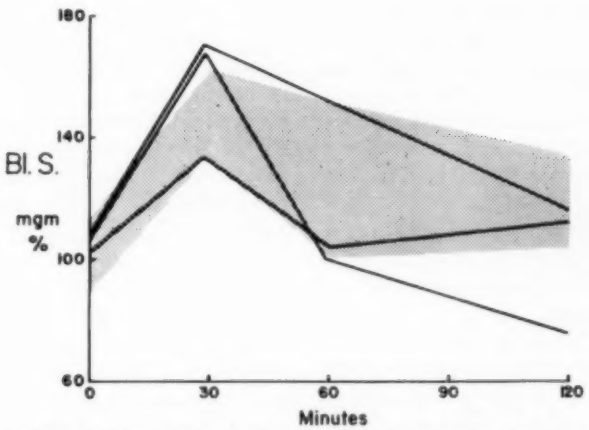

Fig. 3.—Responses of blood sugar during oral glucose tolerance tests in children with muscular dystrophy receiving growth factor. As in the case of the intravenous tolerance studies described in Figure 2, there is no evidence of impairment of carbohydrate metabolism during growth-hormone therapy. The responses in the three patients on growth hormone (solid lines) are compared to the average values obtained in a group of 11 children with muscular dystrophy not receiving growth factor. The responses of the latter group ± 1 S. D. are apparent in the dotted background figure and have been described in a previous publication.[19]

Table IV

PROTEIN-BOUND IODINE IN CHILDREN WITH MUSCULAR DYSTROPHY RECEIVING GROWTH FACTOR THERAPY

Patient	Date	Therapy	PBI gamma %
J.B.	11/7/52	none	6.6
	7/23/53	"	9.3
	7/24/53	growth hormone	
	9/21/53	" "	9.1
	12/3/53	" "	11.9
J.C.	11/7/52	none	6.6
	7/25/53	growth hormone	
	9/24/53	" "	5.9
	11/19/53	" "	9.6
P.D.	5/7/53	none	5.0
	7/31/53	growth hormone	
	8/21/53	" "	5.8
	9/22/53	" "	6.0
J.M.	12/4/52	none	14.3
	5/53	growth hormone	
	8/19/53	" "	4.7
	9/15/53	" "	4.4

Table V

URINARY 17-KETOSTEROID OUTPUT DURING GROWTH FACTOR THERAPY

Patient	Date	Therapy	17-Ketosteroid 24-Hour
J.B.	7/20-21/53	none	2.1
	7/24/53	growth hormone	
	8/19-20/53	" "	.2
	10/19-20/53	" "	5.8
	12/2-3/53	" "	.6
J.C.	11/4-5/52	none	1.7
	7/15-16/52	"	1.6
	7/18-21/53	"	2.1
	7/25/53	growth hormone	
	8/16-17/53	" "	3.2
	9/20-21/53	" "	3.0
	11/18-19/53	" "	2.9
P.D.	3/8-9/53	none	2.5
	4/24-27/53	"	1.0
	4/27-30/53	"	2.0
	4/30-5/3/53	"	1.9
	5/3-4/53	"	1.2
	7/31/53	growth hormone	1.2
	8/20-21/53	" "	2.9
	9/10-11/53	" "	3.4
	9/16-17/53	" "	2.5
	9/20-21/53	" "	2.0
	10/8-9/53	" "	2.0
	12/2-3/53	" "	2.6
J.M.	4/18-19/53	none	1.3
	5/1/53	growth hormone	
	5/12-15/53	" "	
	5/15-16/53	" "	
	9/17-18/53	" "	5.7
	9/20-21/53	" "	6.0
	11/23-25/53	" "	8.5
	11/30-12/1/53	" "	3.1
	12/3-4/53	" "	4.2

Table VI

URINARY GONADOTROPINS DURING GROWTH FACTOR THERAPY

Patient	Date	Therapy	Gonadotropins (6)	(12)	(24)	(48)	(96)
J.B.	7/24/53	growth hormone	-	-	-	-	+
	7/25/53	" "	-	-	-	-	+
	10/14-15/53	" "	-	-	-	-	+
J.C.	11/5/53	none	-	-	-	-	+
	7/25/53	growth hormone	-	-	-	-	+
	9/17-18/53	" "	-	-	-	-	+
P.D.	3/6/53	none	-	-	-	-	+
	7/31/53	growth hormone	-	-	-	-	+
	10/16/53	" "	-	-	-	-	+
J.M.	4/18-19/53	none	-	-	-	-	+
	5/53	growth hormone	-	-	-	-	+
	9/16/53	" "	-	-	-	-	+
	12/11/53	" "	-	-	-	-	+

as well as repeated observations of the prothrombin time, bromsulfalein excretion, serum cephalin flocculation, thymol turbidity, alkaline phosphatase, and free and total bilirubin were all within normal limits during growth-factor therapy.

COMMENT

There is no evidence that this preparation of growth factor altered the muscular debility in these patients. However, a considerable amount of information has been accumulated concerning the properties of this pituitary extract.

It will be recalled that it was administered with impunity for prolonged periods of time. There was no evidence of any diabetogenic property in this preparation, as indicated by glucose and by insulin tolerance tests. It

should be pointed out that species and individual susceptibilities to the diabetogenic properties of pituitary products have been frequently noted.# In some studies a combination of agents, i. e., growth factor and corticotropin, elicited changes in insulin or carbohydrate tolerance.* Finally, it has been observed that the pH of the preparation is important in determining the absence or presence of diabetogenic proprties, i. e., it is lost in alkaline solution.† Our own material, however, had an acid pH.

Serial studies failed to reveal any significant amount of thyroid-, adrenal-, or gonad-stimulating factor in the growth-hormone preparation. The rise in 17-ketosteroids during therapy in J. M. may be attributable to spontaneous maturation of gonads and perhaps adrenal cortices; it was not seen to the same degree in the other three after equally long periods of treatment.

The preparation did contain a factor which stimulated melanophores, since it produced freckling within several days of starting therapy. The failure to observe a cumulative and persistent effect suggests that an unresponsiveness had developed. It has been noted, of course, that some preparations of corticotropin induce freckling of the type seen in clinical Addison's disease, even though it has been suggested that in animals the intermediate lobe of the pituitary is the site of melanophore-factor production.‡ Our findings suggest that the melanophore factor is not necessarily limited to corticotropin preparations and are in keeping with reports that it can be isolated or purified as a separate entity or may be present in other pituitary concentrates.§

The absence of any clear increase in the retention of electrolytes and nitrogen during the balance studies would be in keeping with most but not all of the experiences of other workers || and suggests that stimuli for such retention were already maximal in these four patients. This is not surprising, since their growth and development were not retarded in the sense that they are in pituitary dwarfs. It may be that over a prolonged period some net increment in muscle size or constituents did develop. If this were so, it was not apparent clinically, nor did the body weights increase.

SUMMARY AND CONCLUSIONS

A preparation of pituitary growth factor shown to be active in producing a resumption of growth in immature hypophysectomized mice was given with impunity but without clinical benefit to four children with muscular dystrophy.

Appendix

RESULTS OF BIOASSAY OF GROWTH FACTOR CONDUCTED BY Dr. Gustav Wurtzel OF THE NATIONAL DRUG COMPANY:

ASSAY OF PITUITARY GROWTH FACTOR (Lot G 25-H) IN IMMATURE HYPOPHYSECTOMIZED FEMALE RATS*

Rats #	Growth Factor R_X gamma/day	Mean Body Weight		
		Before R_X gram	Post 10 d. R_X grams	Δ grams
10	10	107.4	118.5	+11.1**
5	none	110.8	109.2	− 1.6

*Intraperitoneal injections started 12 days following hypophysectomy in accordance with Ware et al. JAMA
**Therefore, G 25-H is equivalent to Li growth hormone or Wilhelmi crystalline growth preparation since 10 gamma/day produced a 10 gram weight gain in 10 days. Hence 10 gamma equals 1 unit.

This preparation did not alter insulin or glucose tolerances, nor did it stimulate the thyroid, adrenal cortex, or gonads.

The appearance of crops of freckles in all four subjects shortly after start of treatment points to the presence of a melanophore factor in this preparation.

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Muscular Dystrophy

VIII. Trials of Protein Hydrolysate, Vitamin Supplements, and Physical Therapy

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It has recently been reported that the ingestion of a protein hydrolysate together with a vitamin preparation produces distinct clinical improvement in muscular dystrophy.* A group of children believed to have this disease have therefore been placed on such a regimen. The results have been compared with those obtained with physical therapy alone as well as with the spontaneous changes which occur without hydrolysate and without physical therapy.

MATERIAL AND METHODS

Twenty-nine children afflicted with muscular dystrophy, 2 to 15 years of age, have been seen at intervals by a physical therapist, an orthopedist, and a physician. In all of these patients the diagnosis seems justified by virtue of the findings on physical examination and on biopsy of muscle sections. The details of these observations together with the results of certain biochemical studies of body fluids have been presented earlier.†

Serial measurements of muscle strength have been made in the following three groups of such patients: (*a*) children with muscular dystrophy not under treatment or just receiving vitamins, (*b*) those maintained on protein hydrolysate and vitamin supplements‡ without physical therapy, and, (*c*) children maintained on the protein-hydrolysate-vitamin regimen while receiving physical therapy in variable amounts. Motor strength was measured by evaluating the performance of individual muscle groups against gravity and against resistence and rated in accordance with the scale in Table II. The serial examinations were conducted by the

Table I

PHYSICAL THERAPY PROGRAM FOR CHILDREN WITH MUSCULAR DYSTROPHY

I. EXERCISES TO BE PERFORMED 6 TIMES EACH DAY*

A. Abduct arms to 90 while supine on firm surface with deep breathing

B. Raise legs (straight) from 45 while supine

C. Abduct R. leg in forward plane while lying on left side

D. Abduct R. leg in posterior plane while lying on left side

E. Hyperextend hip with knee straight, R. and L., while prone

F. Extend arms alternately while prone

G. Hyperextend back while prone

H. Abduct L. leg in posterior plane while lying on right side

I. Abduct L. leg in posterior plane while lying on right side

J. Flex trunk while supine, knees flexed and feet braced; this may be actively completed or consist only of assisted neck flexion with trunk at rest in debilitated patients

II. Exercise is placed upon keeping the patients ambulatory or mobile within the limits of fatigue, i.e., patient is to crawl if walking is not possible, roll if crawling is not feasible, and alternate lying positions (prone and supine) with immobile sitting

III. In the hospital the above program is supplemented by the use of hydrotherapy and moist heat

* The number of times each exercise is performed is determined by the patient's ability and the onset of fatigue with 6 as the maximum, the conditions are varied to meet the patient's limitations, i.e., resistance may be applied or assistance given

(In Exercise H, "posterior" should read "forward.")

Submitted for publication Aug. 31, 1955.

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Supported by grants-in-aid from the Muscular Dystrophy Associations of America, Incorporated, and the American Cancer Society.

* References 1 and 2.

† References 3-7.

‡ One heaping teaspoon of Walker protein hydrolysate t. i. d. and 1 capsule of Rubrafolin b. i. d. According to the manufacturer, Walker protein hydrolysate contains the amino acids present in 16 gm. of an enzymatic digest of casein and the following: vitamin A, 5000 U. S. P. units; vitamin D, 500 U. S. P. units; thiamine HCl, 10 mg.; riboflavin, 6 mg.; pyridoxine HCl, 1 mg.; calcium pentothenate, 1 mg.; malinamide, 50 mg.; ascorbic acid, 100 mg.; iron peptonate, 0.1 gm.; and tribasic calcium phosphate, 1.0 gm. Each Squibb Rubrafolin capsule contains 25γ of vitamin B_{12} and 1.67 mg. of folic acid. Walker Laboratories, Inc., and E. R. Squibb & Sons provided generous supplies of hydrolysate and Rubrafolin, respectively.

Table II

MUSCLE STRENGTH IN MUSCULAR DYSTROPHY PATIENTS NOT UNDER TREATMENT OR ON SUPPLEMENTARY VITAMINS ONLY

Patient Age-Sex	Date	Physical Therapy	Hydrolysate	Vitamin Capsule	Muscle Status* Trunk R.	Trunk L.	Abdomen R.	Abdomen L.	Lower Extremities R.	Lower Extremities L.	Neck R.	Neck L.	Upper Extremities R.	Upper Extremities L.	Average	Comments by Family
C.P.	1/21/53	none	none	none	40	40	35	35	46	44	25	25	49	49	40.3	"falls more frequently"
	8/30/54				40	40	40	40	52	50	30	25	50	49	47.8	
B M	2/11/55				35	35	35	35	54	55	25	25	45	48	47.6	
E.D.	4/23/54	none	none		50	50	60	60	46	46	50	50	47	46	42.9	"getting worse can no longer walk"
	4/30/54			1 caps. q.d.												
2 M	9/7/54				30	30	50	50	47	48	30	30	42	47	46.5	
V.B.	4/23/54	none	none		3	3	25	25	44	44	10	10	40	40	37.7	"better appetite, weight gain
	4/30/54			1 caps. b.i.d.												
6 F	9/7/54				3	3	50	80	65	46	10	18	39	40	38.8	
G.P.	1/22/53	none	none	none	25	15	25	15	35	36	25	25	45	44	37.8	"no improvement"
15 M	9/1/54				75	75	35	35	66	64	50	50	66	64	63.8	
D.M.	2/9/53	none	none	6/1/54	10	10	25	20	25	25	20	15	41	42	21.9	"legs more flexible
	6/ /54			1 caps.												
13 M	9/10/54			b.i.d.	0	10	15	15	23	29	15	12	34	37	27.4	

*Graded in accordance with the following table:
N or 100% = NORMAL = function against gravity and normal resistance
G or 75% = GOOD = function against gravity and some resistance
F or 50% = FAIR = function against gravity only
P or 25% = POOR = function in horizontal plane
T or 10% = TRACE = a few fibers have active function
Intermediate grades, i. e., F- or F+ represents an estimated 10 per cent lesser or greater function

same physical therapist without reference to records of previous results.

Finally, in view of possible effects of the protein hydrolysate-vitamin therapy upon serum and blood solutes, samples of venous blood were obtained during the fasting state at intervals of weeks or months. These were analyzed for levels of sugar and nonprotein nitrogen in whole blood and for concentrations of globulin, cholesterol, calcium, sodium, potassium, chloride, and total CO_2 content in serum by methods in regular use in this laboratory.[8]

RESULTS

A. No Hydrolysate or Physical Therapy.—From Table II it is apparent that the family reported improvement only in V. B., who was receiving two vitamin capsules each day; in the remainder there was either no change or further deterioration in the course of 5 to 25 months of observation. On the other hand, objective measurements of motor strength by the physical therapist showed only minor changes in motor power in four of the patients and an actual spontaneous increase in G. P.

B. Protein Hydrolysate and Vitamins Without Physical Therapy.—All patients and their families and friends reported subjective as well as objective improvement at one time or another, but especially shortly after initiating therapy. Also, an awareness of increased warmth and paraesthesia of various types were frequently experienced. None of the patients had any dramatic or definite improvement of the type reported by Van Meter,[1] i. e., recovery of ability to climb stairs, run, etc. Detailed examinations of muscle strength in accordance with the scheme outlined in Table II revealed that, with the exception of patients E. S., and R. M., motor power had not increased (Table III). On the other hand, an increase had been noted in one of the patients receiving no therapy whatsoever (Table II).

C. Protein Hydrolysate, Vitamin Supplement, and Physical Therapy.—In this group, which is larger and has been under observation for a longer period of time, there is defi-

Table III

MUSCLE STRENGTH IN PATIENTS WITH MUSCULAR DYSTROPHY RECEIVING PROTEIN HYDROLYSATE AND VITAMIN SUPPLEMENTS (No Physical Therapy)

Patient Age-Sex	Date	Physical Therapy	Hydrolysate	Vitamin Capsule	Muscle Status Trunk R.	Trunk L.	Abdomen R.	Abdomen L.	Lower Extremities R.	Lower Extremities L.	Neck R.	Neck L.	Upper Extremities R.	Upper Extremities L.	Average	Comments by Family
S.E.	11/9/53	none	12/8/53:	12/8/53:	60	60	60	60	62	61	20	20	66	68	60.7	"arms stronger"
	12/8/53		tsp. b.i.d.	1 caps. b.i.d.												
	1/9/54				40	40	35	35	54	50	30	20	55	60	55.6	
	4/3/54				45	40	35	35	56	58	30	20	56	59	50.1	
	9/1/54				40	40	35	35	53	53	30	20	48	54	52.5	
B M	2/1/55				35	35	15	15	46	45	20	20	52	51	46.9	
E.S.	2/27/53	none	12/4/53:	12/4/53:	35	35	35	35	56	53	25	20	49	51	49.1	"muscles stronger, falls less"
	12/4/53		tsp. b.i.d.	1 caps. b.i.d.												
15 M	9/1/54				75	75	35	35	60	64	50	50	66	64	63.8	
S.F.	2/25/54	none	3/1/54:	3/1/54:	25	25	15	15	42	47	15	15	49	48	43.1	"hands stronger, can get in and out of walker"
	3/13/54		tsp. b.i.d.	1 caps. b.i.d.												
	9/10/54				12	12	15	15	38	38	15	13	43	40	30.6	
14 M	2/8/55				12	12	25	25	34	39	20	20	43	43	30.8	
J.G.	?	none	12/1/53:	12/1/53:	15	15	25	15	36	40	25	25	50	47	42.8	"not progressing, but no improvement
	7/15/53		tsp. b.i.d.	1 caps. b.i.d.	15	10	25	25	36	40	20	20	44	43	29.9	
	11/18/53				10	10	25	25	35	35	15	15	45	30	30.7	
	11/18/53				3	3	15	15	30	40	15	15	43	41	27.0	
	9/3/54				5	5	25	25	30	34	20	15	41	40	30.7	
11 M	2/9/55															
R.M.	12/1/53	none	12/1/53:	12/1/53:	0	0	5	5	6	6	12	13	7	8	6.7	"hands stronger"
	12/12/53		tsp. b.i.d.	1 caps. b.i.d.	3	3	15	15	20	17	5	5	28	28	21.5	
	9/7/54				3	3	15	15	14	13	5	5	27	25	18.5	
	2/11/55															

Table IV

MUSCLE STRENGTH PRIOR TO AND DURING A REGIMEN OF PHYSICAL THERAPY AND DAILY ADMINISTRATION OF PROTEIN HYDROLYSATE AND VITAMIN SUPPLEMENTS

Patient Age-Sex	Date	Physical Therapy		Hydrolysate	Vitamin Capsule	Muscle Status										Comments by Family
		Home	Clinic			Trunk		Abdomen		Lower Extremities		Neck		Upper Extremities		Average
						R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	
L.K.	9/ /53	1 hr q.d.	1 hr q.wk	11/30/53: tsp. t.i.d.	11/30/53: caps. b.i.d.	25	25	100	100	73	73	72	72	77	81	76.0
	11/10/53															"less nervous"
	11/26/53					25	25	75	75	71	76	50	50	80	78	74.1
	6/31/54					25	25	100	100	86	86	68	68	85	88	85.8
14 M	1/4/55					23	22	100	100	86	82	62	62	87	85	81.0
E.R.	11/11/52	1/2 hr q.d.	irreg.	12/15/53: tsp. t.i.d.	12/15/53: caps. q.d.	75	75	35	35	64	64	35	35	70	71	65.1
	12/15/53															"improvement in muscles of calves and arms"
	12/19/53					75	75	75	75	59	66	25	25	64	66	63.6
	2/27/54					65	65	25	25	68	61	30	30	71	68	62.9
8 M	8/30/54					65	65	20	20	62	62	20	20	68	68	62.6
J.C.	11/10/52	1 hr q.d.	1 hr q.wk	1/26/54: tsp. t.i.d.	1/26/54: caps. t.i.d.	60	60	35	35	69	68	45	45	62	59	54.3
	7/9/53					60	65	40	30	51	51	45	50	66	65	58.2
	10/30/53					75	75	25	25	44	44	50	50	69	66	55.0
	12/22/53					60	65	25	25	52	58	60	60	70	73	62.0
	1/23/54					60	65	25	25	48	48	60	60	72	70	58.9
	1/24/54															
	6/30/54					65	65	25	25	58	51	55	60	72	72	61.2
	9/9/54					60	60	25	25	51	59	55	60	68	67	58.0
6 M	2/17/55					60	60	25	25	47	66	65	45	67	66	55.9
E.R.	10/20/52	1 hr q.d.	1 hr q.2 wks	11/15/53: tsp. t.i.d.	11/15/53: caps. b.i.d.	85	85	45	45	71	71	25	25	75	75	71.8
	7/14/53					85	85	50	50	73	73	35	35	77	77	72.0
	11/5/53					75	75	50	50	60	60	30	25	63	61	58.5
	2/11/54					60	65	60	60	58	58	30	30	61	58	57.8
	8/12/54					50	50	60	60	64	64	35	35	65	64	62.4
8 M	1/28/55															
C.W.	12/7/53	1 hr q.d.	1 hr q.wk	12/1/53: tsp. t.i.d.	12/1/53: caps. b.i.d.	25	25	75	75	64	67	30	20	51	58	56.7
	12/7/53					60	60	50	50	67	67	20	12	62	65	62.7
	2/15/54					40	40	35	30	60	58	20	12	59	63	56.0
	5/16/54					40	40	45	45	62	61	15	12	58	60	57.4
7 M	2/14/55															"more energetic"
T.W.	2/26/53	1 hr q.d.	1 hr q.2 wks	11/15/53: tsp. t.i.d.	11/15/53: caps. b.i.d.	65	65	40	40	71	71	25	25	62	61	60.1
	11/5/53					75	75	35	35	68	66	20	20	63	61	61.1
	11/10/53															"has not progressed"
	4/2/54					50	50	30	35	51	54	35	35	56	60	55.3
	8/31/54					50	50	50	50	53	54	25	35	52	54	52.1
7 M	2/10/55					40	40	38	38	54	54	15	25	53	55	52.1
T.S.	11/21/52	1 hr q.d.	0	6/10/54: tsp. t.i.d.	6/10/54: caps. b.i.d.	25	25	35	35	46	43	43	45	60	60	51.2
						35	35	35	35	58	60	43	45	57	55	50.8
	11/13/53					35	35	35	35	58	62	50	50	57	57	53.0
	5/4/54					35	35	35	35	59	56	40	40	60	59	56.5
	6/10/54															
15 F	9/2/54					25	25	40	40	56	54	38	38	56	56	52.3
E.S.	7/11/53	1 hr q.d.	1 hr q.wk	2/15/54: tsp. t.i.d.	2/15/54: caps. b.i.d.	50	50	25	25	53	54	25	25	58	58	54.0
	8/21/53					50	50	25	25	41	51	20	20	54	55	49.8
	2/26/54					35	35	25	25	39	44	25	25	53	49	45.0
	5/11/54															
	9/1/54					35	35	40	40	51	56	25	25	54	55	50.8
12 F	2/16/55					35	35	35	35	54	54	25	25	53	51	50.4
T.N.	2/17/53	1 hr q.wk	1 hr q.wk	12/1/53: tsp. q.d.	12/1/53: caps. b.i.d.	25	25	25	25	50	64	35	32	54	53	47.6
	11/12/53					25	25	15	15	33	40	25	25	44	42	37.7
	11/21/53															"no improvement, poor appetite"
	3/11/54					15	15	25	25	43	43	20	20	45	45	46.4
	9/3/54					10	10	15	15	29	25	20	20	37	36	30.0
8 M	2/18/55					13	13	35	30	40	40	20	20	40	37	36.5
W.S.	11/10/52	1/2 hr q.d.	0	12/15/53: tsp. t.i.d.	12/15/53: caps. b.i.d.	35	35	30	30	30	32	30	30	45	44	37.5
	12/15/53															"slight improvement"
	12/19/53					35	35	20	20	21	32	25	30	42	48	31.4
	2/27/54					25	25	15	15	27	25	25	25	43	41	33.2
14 M	8/30/54					13	12	25	25	20	20	15	15	41	42	29.6
D.M.	2/20/54	1/2 hr q.d.	0	2/1/54: tsp. t.i.d.	12/15/53: caps.	10	10	15	15	26	26	20	20	45	43	34.3
	7/2/54					5	5	15	15	32	30	20	20	37	39	31.9
14 M	8/31/54					3	3	12	13	27	34	20	15	30	40	30.0
D.H.	11/8/53	1 hr q.d.	1 hr q.wk	6/1/54: tsp. t.i.d.	6/1/54: caps. b.i.d.	100	80	75	75	80	82	32	32	85	89	80.9
	3/11/54															"has not progressed"
8 F	8/2/54					100	100	50	50	78	78	42	42	80	79	78.1
D.H.	11/6/53	1 hr q.d.	1 hr q.wk	tsp. t.i.d.	6/1/54: caps. b.i.d.	50	50	40	40	71	70	45	45	75	75	70.0
	3/11/54															"appetite improved"
	8/2/54					40	40	75	75	66	62	40	40	60	62	60.2
13 F	2/10/55					35	35	50	50	62	63	45	45	63	60	50.0
J.B.	7/3/52	1/2 hr q.d.	irreg.	1/15/54: tsp. t.i.d.	1/15/54: caps. b.i.d.	3	0	20	20	32	33	30	20	34	37	32.4
	1/8/53					3	0	20	20	33	35	30	30	35	37	32.9
	10/7/53					18	18	30	30	29	32	25	25	38	36	32.5
	1/14/54															"improving a little"
	1/21/54					10	10	30	30	26	27	25	25	34	35	30.4
	7/15/54					10	12	25	25	28	27	20	20	35	34	28.6
4 M	9/9/54					12	12	25	25	24	24	12	15	34	33	27.3
G.T.	9/1/54	1/4 hr q.d.	1 hr q.wk	9/4/54: tsp. t.i.d.	9/4/54: caps.	75	75	25	25	66	64	50	50	66	64	63.3
13 M	2/7/55					75	75	75	75	66	66	45	40	64	62	64.8
G.E.	2/6/53	1 hr q.d.	1 hr q.wk	1/15/54: tsp. t.i.d.	1/15/54: caps. b.i.d.	-	-	40	40	46	45	25	25	62	55	32.3
	1/16/54					15	35	25	25	35	32	15	15	50	46	30.8
	3/13/54					15	25	25	25	30	30	15	15	47	43	30.4
9 M	6/17/54					18	25	20	25	41	37	13	14	44	44	28.7
H.S.	3/6/53	?	1 hr q.wk	2/23/54: tsp. t.i.d.	2/23/54: caps. b.i.d.	50	50	35	35	44	47	35	35	48	48	46.8
	11/17/53					40	50	25	25	45	46	25	25	49	46	40.2
	3/23/54					50	50	50	50	45	48	30	25	46	47	45.2
9 M	7/16/54					40	40	75	75	50	52	30	35	53	53	51.9
W.S.	2/6/53	?	1 hr q.wk	2/23/54: tsp. t.i.d.	2/23/54: caps. b.i.d.	60	60	40	40	61	64	40	40	63	64	59.4
	11/10/53					60	60	40	40	54	55	35	40	59	59	55.5
	3/30/54					60	70	60	60	49	48	35	35	47	48	47.8
8 M	7/9/54					60	60	65	65	52	50	35	35	47	49	49.6
C.E.	2/27/53	1/3 hr q.d.	0	11/20/53: tsp. t.i.d.	11/20/53: caps. b.i.d.	25	25	25	25	39	39	35	35	58	56	46.9
	11/6/53					25	35	25	25	40	42	25	25	52	54	45.4
11 M	3/30/54					15	15	35	35	40	37	20	25	42	42	29.1
J.M.	4/5/54	1/4 hr q.d.	0	6/7/54: tsp. t.i.d.	6/7/54: caps. b.i.d.	60	60	65	65	61	60	60	60	69	70	65.0
	4/29/54					60	60	60	60	62	60	45	45	70	69	63.0
	7/9/54					50	50	60	60	55	57	35	50	67	67	60.7
10 M																

nite evidence of progression of the disease in a number of the children despite combined therapy and in the face of family reports of improvement (Table IV). Thus losses of extremity strength seem to have occurred in patients E. R., T. W., T. N., K. S., and W. S. In L. K., J. C., G. W., and T. S. a slight increase in arm and leg power, or both, was recorded. However, in no patient was there any persistent increase in trunk muscle power, and actual decreases were found in about one-half.

Table V

SUMMARY OF SERUM SOLUTES IN MUSCULAR DYSTROPHIC CHILDREN ON PROTEIN HYDROLYSATE COMPARED TO NORMALS

	Age (years)	Muscular Dystrophy Mean ± S.D. (#)	Normals Mean ± S.D. (#)
HCO_3 (mEq/l)	3.5 - 18.0	22.9 ± 3.8 (67)	22.1 ± 1.3 (125)
Cl "	" "	102.6 ± 3.6 (60)	103.3 ± 3.0 (108)
Na "	" "	143 ± 3 (80)	144 ± 3 (108)
K "	" "	4.5 ± 0.3 (78)	4.37 ± 0.40 (142)
Prot. (gm%)	" "	7.10 ± 0.50 (65)	7.27 ± 0.57 (49)
Alb. "	" "	4.26 ± 0.57 (63)	4.28 ± 0.58 (47)
Glob. "	" "	2.95 ± 0.49 (63)	3.00 ± 0.55 (47)
Ca (mg%)	" "	10.38* ± 0.59 (63)	9.82 ± 0.43 (48)
Phos. "	3.5 - 12.9	5.34* ± 0.64 (53)	4.72 ± 0.41 (48)
Phos. "	12.5 - 18.0	5.21* ± 0.94 (22)	4.36 ± 0.60 (47)
Chol. "	3.5 - 18.0	260 ± 66 (56)	220 ± 43 (105)

* Differences are statistically significant. "p" values were less than 0.0001

D. Serum and Blood Solutes with Protein Hydrolysate and Vitamins, With or Without Physical Therapy.—The results of repeated analyses of blood and serum presented in Table V indicate that the addition of protein hydrolysate to the regimen in general produced no change in the blood and serum solutes tested. The higher levels of serum calcium and inorganic phosphorus described in an earlier paper [8] persisted throughout therapy. The mean chloride and cholesterol levels which prior to therapy were lower in muscular dystrophy children compared to healthy controls rose to levels indistinguishable from those seen in normals.

COMMENT

Serial examinations of motor strength in children with muscular dystrophy indicated that deterioration had occurred in some of the patients irrespective of whether or not they received hydrolysate and extra vitamins alone or in conjunction with physical therapy during intervals up to one year or more in length. This is in keeping with the experience of others.§ In any such study the degree of adherence to the prescribed regimen can only be estimated. Nonetheless, careful questioning and checking indicated that the recorded estimates are reasonably correct. In the case of the patients treated with hydrolysate and vitamins the rate of replenishment of gratis supplies of these materials provided an additional indication of probable dosage schedules.

§ References 9 and 10. Milhorat, A.: Personal communication to the authors. Mason, H.: Personal communication to the authors.

The study has not yet been pursued long enough for us to be certain whether or not the rate of deterioration was altered by the regimens employed. However, we do know that none of the patients responded to the protein hydrolysate and vitamin supplementary with dramatic improvement. Every attempt was made to duplicate the treatment program of Van Meter [1] by using products from the same manufacturer and on the same dosage schedule. All of the patients either knew of the beneficial results reported or read the original report. Placebo trials were not made. The favorable reports of the families might well represent optimism engendered by the new treatment, the solicitous attention, and wishful thinking.

The comments of the physical therapists participating in this study, made spontaneously at the end of two years of experience, suggest another possible resolution of the discrepancy between the improvement often reported by the patients and their families and friends and the lack of concomitant increase in objective motor strength. The physical therapists noted that those patients who were ambulatory had developed peculiarities of gait and of posture which permitted maximum utilization of their remaining muscular strength. Encouragement engendered by these regimens with or without physical therapy made them more adept in this regard and as a consequence led the family to the unsubstantiated belief that muscle strength had actually increased. However, this view is advanced with reservations, since many problems were recognized in the serial muscle tests. The physical therapists pointed out, for example, that they had to acquire a special proficiency in this type of testing. This necessitated (*a*) recognition of and making proper allowance for the fact that the isolated lives of these patients do not permit facile communication with strangers, (*b*) avoidance of maneuvers which might prove painful, since the patients complain of pain far more readily than children with other types of muscular involvement, (*c*) proper appreciation of the fact that affected muscles appear to be capable of only one maximum contraction after

an adequate recovery period, and (*d*) avoidance of any procedure in testing, in instruction, or in physiotherapy which would upset the finely adjusted equilibrium of the ambulatory patients. With regard to this last point, it should be emphasized that heavy braces must not be used. One of the children studied, G. Z., was fitted with cumbersome braces elsewhere and promptly ceased walking. Replacement of these with light aluminum splints which are applied only at night and intensive physical therapy here remobilized him. An additional interesting observation has been made relative to other factors in continued ambulation. It has been noted that these children who have flat feet or eversion continue to walk in a normal manner, whereas those who have good arches go into an equinus position.

There was no evidence that the hydrolysate-vitamin regimen altered the relative hyperphosphatemia and hypercalcemia which appear to be present in muscular dystrophy.[5] Serum chloride levels did rise, and the relative hypochloremia present in these patients prior to therapy disappeared. This could be the result of a greater intake of this electrolyte made possible by the daily ingestion of the protein hydrolysate. We have no additional explanation for the similar change in serum cholesterol levels.

SUMMARY AND CONCLUSIONS

Serial measurements in children with muscular dystrophy revealed losses of motor power during prolonged observation despite a regimen of protein hydrolysate and vitamin supplementation, with or without physical therapy, during periods up to one year or more in length. Occasional slight improvement recorded during such therapy was also noted in one of the patients under observation without any treatment whatsoever.

The favorable reports obtained from the patients and their families suggesting improvement during one or the other of the regimens represented optimistic hope or possibly the acquisition of a greater skill through physical therapy and encouragement in using remaining motor strength.

Our data do not permit us to decide at this time whether the rate of deterioration was altered during any of the regimens tested.

The importance of not interfering with patient's own postural or functional adjustments to his disability became evident during the course of the serial visits for muscle treatment and examination.

The protein hydrolysate and vitamins did not discernibly alter the somewhat elevated fasting levels of serum calcium and phosphorus previously shown to be present in children with muscular dystrophy.

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Prednisone in the Treatment of Allergic Disorders in Children

Observations of Plasma 17-Hydroxycorticosteroid Levels

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The steroids and corticotropin have become recognized and generally accepted as valuable adjuncts in the treatment of most allergic conditions. Their limitations and their frequent side-effects, particularly with the prolonged use of these hormones, have been well defined in previous publications.* Recently two new steroids, prednisone † (Meticorten) and prednisolone ‡ (Meticortelone), have been recommended in the treatment of many types of allergic disorders because of their greater antiinflammatory potency and fewer side-reactions. Some of the first reports of these new hormones described their use in the treatment of rheumatoid arthritis.§ Subsequently, several investigators found prednisone to be equally effective in the treatment of bronchial asthma and other atopic allergic conditions.‖ These latter papers, however, reported on the use of prednisone in the treatment of adults.

The purpose of the present communication is to report our clinical experience using prednisone in a small series of allergic children and to present our findings on plasma 17-hydroxycorticosteroid (17-OHCS) levels in some of these patients while they were undergoing therapy with this new drug.

METHODS

Sixteen patients were selected from the pediatric allergy clinic at Harbor General Hospital, Los Angeles, and from private practice. All of these children, most of whom had bronchial asthma, were difficult cases who had not responded to ordinary allergic management. Some of them had been treated with other steroid hormones in the past. During our early experience with this new steroid, a low-salt diet and added potassium in the form of potassium iodide or potassium citrate were recommended. When it was observed, however, that no visible edema or changes in serum sodium or potassium levels developed, these precautionary measures were discontinued. All patients were seen twice a week, at which time their weight, blood pressure, and clinical status were determined. Routine urinalyses and blood cell counts were done every few weeks. Periodically, and when a change in the patient's status was noted, blood was drawn for plasma 17-OHCS and total eosinophile counts. The 17-OHCS plasma levels were determined by the method of Nelson and Samuels.[10] Control levels were similarly determined in other allergic and nonallergic children who were not given prednisone. The results of these other determinations will be reported in a subsequent publication.

On the basis of the original report by Bunim and co-workers [4] that prednisone was three to five times as potent in its antiinflammatory action as cortisone, the initial or suppressive dose of the drug in the present study was arbitrarily set at 15 to 20 mg., given in divided doses, three to four times daily. This dose was maintained until the patient was completely free of symptoms and was then gradually reduced 2.5 mg. every three to four days until symp-

Submitted for publication Dec. 20, 1955.

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Prednisone (Meticorten) was furnished through the courtesy of the Schering Corporation, Bloomfield, N. J.

This study was supported in part by a grant from the Attending Staff Association of Harbor General Hospital, Torrance, Calif.

* References 1-3.

† Prednisone, formerly known by the generic name metacortandracin.

‡ Prednisolone, formerly known by the generic name metacortandralone.

§ References 4-6.

‖ References 7-9.

toms recurred. This process was repeated several times in order to determine which maintenance dose was suitable for each individual patient.

RESULTS

Sixteen patients were treated with prednisone for periods varying from 1 to 22 weeks. Most of them are still receiving this hormone so that they may be observed for longer periods of time. With one exception, the results of this drug in producing a clinical remission were quite dramatic. Within 24 to 48 hours on initial suppressive dosages, as indicated in Table 1, the patients improved markedly and the allergic symptoms abated.

TABLE 1.—*Results of Prednisone Therapy*

Case	Age, Yr.	Duration of Therapy, Wk.	Diagnosis*	Suppressive Dose, Mg.	Maintenance Dose, Mg./24 Hr.	Initial Wt., Lb.	Wt. Gain, Lb.
1	8	3	BA	20	15	57	8†
2	1 9/12	14	AE	15	12.5-15	26.5	4
3	7½	14	BA	20	10-15	47	9½
4	6½	11	BA	30	10-15	40.7	7½
5	8	5	BA	20	Not definitely estab.	63.5	2
6	4	22	BA	20	5-7.5	36.5	2
7	5	17	BA	15-20	7.5	45	3¾
8	7½	13	BA	20	7.5-10	48	4½
9	5	14	BA	20	10-12.5	59	7
10	1	15	BA & AE	7.5-10	2.5-5	18.5	½
11	7/12	11	BA	7.5	5-7.5	13	2
12	11½	8	BA	20	10-15	70	6
13	5½	1	BA	20-40	..	34	2¼
14	8	13	BA	20	10	54	0
15	11	9	BA	20	10	75	6
16	2½	5	BA	15	5	33	0

* BA indicates bronchial asthma; AE, atopic eczema.
† This patient developed acute glomerulonephritis, and the weight gain was not entirely due to prednisone.

The only child who failed to respond adequately to large suppressive doses of prednisone was Case 13, a 5½-year-old boy who had been receiving 40 mg. daily. The maintenance dose that was required to keep each patient free of symptoms is also shown in Table 1. As would be expected, this dose varied with the age and weight of the patient as well as with the severity of the allergy. Our results tend to confirm previous reports that prednisone is three to five times more potent in its antiallergic properties than cortisone.

Plasma 17-OHCS levels were followed in 10 of the subjects. A total of 35 determinations was done while they were taking prednisone and 25 control determinations while receiving no drug. These results are shown in Table 2. An analysis of variance of these levels irrespective of whether the patients were taking prednisone demonstrated no significant variability, thus permitting the data to be analyzed further. In order to determine whether there was any correlation between drug dosage and plasma 17-OHCS levels, the latter were determined in each of several patients while receiving 10 mg. or less of prednisone, again while receiving 12.5 to 15 mg., and finally while receiving 20 mg. or more (Table 2). An analysis of variance of plasma steroid level values for the three dosage ranges was not significant, thereby permitting a further statistical test among the mean steroid levels of the three groups. The results of this analysis are shown in Tables 3 and 4. It appears that even in this small series of patients the mean levels of the 17-OHCS vary directly with the dosage of the drug. However, when 17-OHCS levels taken in the group receiving 15 mg. of prednisone or less were compared to those given no steroid medications, significant differences were not observed. Possible explanations for this seemingly paradoxical finding will be given in the discussion. When blood steroid levels of the patients receiving 20 mg. or more of prednisone were statistically compared to the control determinations, a cal-

TABLE 2.—*17-Hydroxycorticosteroid Levels and Clinical Status in Patients Receiving Prednisone and Not Receiving Prednisone*

	Not Receiving Prednisone		Receiving Prednisone		
Case	Clinical Status	17-OHCS, γ/100 Cc.	Clinical Status	Amount of Prednisone, Mg.	17-OHCS, γ/100 Cc.
1	Symp.	2.0	Asymp.	20	15.0
	Asymp.	5.0			
	Asymp.	7.8			
	Asymp.	10.0			
	Symp.	8.9			
	Symp.	4.2			
2	Symp.	7.8	Symp.	12.5	18.0
			Symp.	15	11.2
			Asymp.	12.5	7.0
			Symp.	12.5	0.0
3	Symp.	4.2	Asymp.	20	20.0
	Symp.	13.9	Asymp.	15	18.6
			Symp.	7.5	11.9
			Symp.	10	8.3
4	Symp.	12.2	Asymp.	30	26.9
			Symp.	10	14.1
			Symp.	15	10.1
			Asymp.	20	14.6
			Asymp.	15	0.6
			Symp.	7.5	6.7
			Symp.	10	16.3
5	Asymp.	4.8	Asymp.	20	13.7
	Symp.	1.4	Asymp.	5	0.0
	Asymp.	2.9			
6	Symp.	17.8	Asymp.	15	11.3
	Symp.	9.5	Symp.	5	0.0
			Asymp.	12.5	0.0
			Symp.	7.5	0.0
			Asymp.	10	0.0
7	Symp.	25.2	Asymp.	7.5	1.8
	Asymp.	1.8	Symp.	7.5	6.0
	Symp.	0.0	Symp.	5	4.1
			Symp.	15	4.4
			Asymp.	10	0.0
			Symp.	5	4.1
8	Symp.	0.0	Symp.	10	0.0
			Asymp.	10	0.0
			Asymp.	15	21.4
9	Asymp.	12.7	Asymp.	15	17.7
	Symp.	0.0	Symp.	7.5	0.0
	Symp.	0.0	Symp.	10	0.0
	Symp.	2.4			
10	Symp.	0.0			
	Symp.	3.6			

culated *t*-score of 2.78 and *P*-value of less than 0.01 was found, indicating a highly significant difference. A further analysis of drug dosage as correlated with steroid level yielded a Pearson product-moment *r* of 0.68. A test of the significance of this value indicates that there is very likely a meaningful degree of correlation between the dosage of prednisone and the 17-OHCS levels. Finally, the 17-OHCS levels did not reflect the clinical status of the patient. There was no significant statistical difference between those children with symptoms and those without symptoms as correlated with the 17-OHCS levels.

COMPLICATIONS FROM PREDNISONE

Although none of the patients studied to date has been followed long enough to determine whether the side-effects of prolonged steroid therapy will become evident, the results of treatment over relatively short periods of time have been very encouraging. No serious complications that could be attributed to the administration of the drug have been encountered in any patient. Most of the subjects gained some weight, which was partly ascribed to the voracious appetites that these children developed. Some of the weight increase, however, was probably due to sodium and water retention, for when the drug was decreased in dosage or temporarily discontinued there was often a correspondingly rapid decrease in the patient's weight. Rounding of the facies was observed in most of the children requiring more than 7.5 to 10 mg. a day. Sodium and potassium serum levels were followed in four patients, and no changes were found. Periodic upper-gastrointestinal roentgen studies were also normal in these same four patients. No changes were observed in blood pressures, urinalyses, hemoglobin levels, or leucocyte counts.

One patient, Case 1, developed acute glomerulonephritis while taking 15 mg. of

TABLE 3.—*Comparison of Plasma 17-OHCS Levels to Dosage Levels*

Mg. of Prednisone per 24 Hr. by Mouth	Plasma 17-OHCS γ/100 Ml. Mean Levels	Sample Size	S. E. M.
10	4.31	18	±1.02
12-15	10.52	12	±5.36
More than 20	18.04	5	±6.11

TABLE 4.—*Comparison of Plasma 17-OHCS Levels in Three Dosage Range Groups, 10Mg. or Less, 12.5-15 Mg., and 20 Mg. or More*

Mg. of Prednisone	*t*	*P*
Less than 10 versus 12.5-15	2.30	More than 0.05
Less than 10 versus 20 or more	5.08	More than 0.001
Less than 12.5-15 versus 20 or more	2.22	More than 0.05

prednisone daily. Since no similar type of case report has been found in the current literature and since the sequence of events in this boy's case could also conceivably be due to a toxic reaction to prednisone, his history and findings will be reported in detail in a separate publication.

COMMENT

There can be no doubt that prednisone is an extremely potent weapon in the treatment of allergic disorders of children as well as of adults. Although somewhat dependent on the age, weight, and severity of the disease, the dosage required to suppress the allergy initially and for maintenance was found to be relatively high as compared to that reported in adults. This finding is in agreement with the results found with the use of other corticosteroids in children.[11] A suppressive dose of 20 mg. seemed to be adequate for most of the older children, and the maintenance dose varied from 5 mg. in a one-year-old child up to 15 mg. in the older children.

The plasma 17-OHCS levels taken while the patients were given varying dosages of prednisone were shown to be statistically highly correlated with the amount of the drug taken; that is, the greater the dose of prednisone, the higher was the plasma 17-OHCS level. Similar observations have been reported following the administration of cortisone and corticotropin (ACTH).[12] Since the Nelson and Samuels method is not specific for Compound F but measures all steroids with the 17, 21-dihydroxy-20-ketosteroid configuration, the plasma concentration of 17-OHCS determined by this method reflects both the endogenous and the exogenous corticosteroids present in the plasma. Prednisone has the above configuration in its structure and would therefore be expected to be measured by the Nelson and Samuels method. Furthermore, it has been demonstrated that free prednisone in plasma is measured by this technique.¶ Finally, it is conceivable that prednisone is converted to Compound E before it is completely reduced to the form in which it is conjugated in the body. It would therefore be possible that some of the material measured as 17-OHCS following the administration of prednisone is Compound E which has arisen from the exogenous prednisone.

When the levels of 17-OHCS taken in patients receiving 15 mg. or less of prednisone were compared to levels taken before they were given any steroids there was no significant difference. There could be several reasons for this apparent paradoxical finding. First, from data obtained on plasma 17-OHCS steroid levels in a much larger series of allergic children in various stages of severity of their diseases, the authors have found that when the patient is under stress, e. g., having a severe attack of asthma, his endogenous plasma 17-OHCS rises.# This accounts for some of the elevated 17-OHCS levels in the control series. Secondly, it is well known that many factors other than the administration of the steroids control the plasma level of Compound F in the blood.[13] The adrenocorticotropic hormone is the most important of these. Since the production of this hormone is suppressed by the administration of prednisone, the endogenous secretion of adrenal 17-OHCS in turn is suppressed.[14] Therefore, measurements of 17-OHCS might primarily be measurements of exogenous hormones. Since specimens of the steroids were drawn at variable times after the drug was administered, further discrepancies at the lower dosage levels would be expected. Finally, similar results were found by one of us when 17-OHCS levels were measured in patients receiving cortisone or corticotropin.[12] Mean levels of plasma 17-OHCS of patients receiving 50 mg. of cortisone or less or 40 units of corticotropin were not significantly greater than control values.

In this small series of patients no correlation between asymptomatic and symptomatic states of the patient and 17-OHCS levels could be determined. We had anticipated that a certain critical level of hormone might exist at which most patients would become

¶ Unpublished data.

Data to be published.

asymptomatic. It appears that many factors other than plasma levels of 17-OHCS determine the severity of an allergic condition, since we were unable to show this correlation by the methods employed. Clinically, the dosage of prednisone necessary to maintain the patient in an asymptomatic state was usually in the range of 2.5 to 5 mg. daily. This small amount of drug was not reflected in the plasma 17-OHCS levels.

Although prednisone proved to be extremely effective in controlling the allergic manifestations in this small series of patients, it must again be emphasized that we still do not know what toxic effects might result from the prolonged use of this drug. One group of investigators has already encountered peptic ulcers in three patients, and one of their cases developed a severe depressive psychosis.[15] It is not unlikely that further reports of the more serious types of side-reactions with the prolonged use of this drug will shortly appear in the literature. Until further information is available on the long-term use of prednisone, we advise that all of the precautions that are applicable to the use of cortisone, with the possible exception of supplementing the diet with potassium and restricting sodium, be applied to prednisone. Furthermore, the drug should only be used in chronically ill and severely allergic patients who have failed to respond to the accepted treatment of allergic diseases. Finally, prednisone should not be used as a substitute for other accepted measures of allergic therapy but used in conjunction with them.

SUMMARY AND CONCLUSIONS

The results in 16 allergic children ranging in age from 7 months to 11 years treated with prednisone, a new synthetic steroid, are reported. Dosages for suppression (15-30 mg.) and maintenance (5-15 mg.) were comparable to adult dosages. With these dosages, prednisone was found to be highly effective in the temporary symptomatic relief of asthma and atopic eczema. Plasma 17-OHCS levels showed a highly significant statistical correlation with the amount of drug taken at high dosage levels, but not with the clinical status of the patient. No serious side-effects were observed in any of the children treated, but the majority had evidence of some sodium and water retention and rounding of the facies. One patient developed acute glomerulonephritis while receiving prednisone. We emphasize that the possible complications or side-effects from the prolonged use of this drug have as yet to be defined and therefore suggest that the precautions that have been recommended for use of cortisone and hydrocortisone, with the possible exception of restriction of sodium and addition of potassium in the diet, be applied to the use of prednisone.

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News and Comment

GENERAL NEWS

German Medical Journal.—Many American students have wrestled with their college German to translate articles in the *Deutsche medizinische Wochenschrift*. It is of particular interest, therefore, that an English language edition has now appeared entitled the *German Medical Journal*. The publishers are to be congratulated for bringing out this edition, which will give a general picture of German medical science and practice to the English speaking physicians of the world. Their aim is well defined in an editorial in the original issue, which states in part:

> If the multiplication of medical periodicals, accompanied by an ever greater departmentalization, has given rise to much concern, the problem is further complicated and even more serious with respect to the international exchange of medical information. Not even multilingual summaries can altogether bridge the language gulf. The German medical profession, after almost two decades of partial isolation for other reasons, has been particularly conscious of this additional language barrier. It is hoped that the GERMAN MEDICAL JOURNAL will be looked upon as an effort to facilitate the exchange of medical advances and experiences between other countries and Germany. English is now understood, if not spoken, by many doctors in most parts of the world and can therefore serve as a natural common language.
>
> It is our aim to make the GERMAN MEDICAL JOURNAL representative of a large segment of German medicine and, at the same time, provide directly or indirectly a forum and a means for the informal exchange of medical knowledge.

We are happy to welcome this new journal, and can assure the editors of its real contribution to the world's medical education

An Attempt to Elucidate the Cause of Growth Retardation in Renal Disease

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Although chronic renal disease is well known as one of the most frequent causes of growth retardation in children, details of the nature of the dependence of growth on kidney function have received little attention. It is obvious that when renal disease has become advanced, the complication of renal rickets provides an explanation for growth retardation, and it is on the marked dwarfism associated with this complication that pediatric texts and treatises on growth and development usually focus attention. The retardation of growth frequently seen in renal disease in the absence of rickets has not, to our knowledge, been specifically studied.

The growth failure of renal disease is usually classed as dwarfism associated with metabolic or organic disorder,* a category into which also fall growth failures resulting from heart disease, liver disease and such diseases of the intestine as celiac disease, pancreatic fibrosis, and megacolon. With the latter diseases, the cause of the retardation is fairly obvious. In heart disease, interference with normal oxygenation of tissues is usually cited as the reason for stunting. Indeed, Campbell and Reynolds [3] have shown a fair correlation between the severity of the cyanosis in congenital heart disease and the degree of growth retardation, although patients with Fallot's tetrad seemed to be less stunted for the degree of cyanosis than patients with other types of deformity. In liver disease, mucoviscidosis, celiac disease, and Hirschsprung's disease, the retardation can be ascribed with fair certainty to undernutrition resulting from failure of normal absorption or metabolism of nutrients.

Explanations for the growth retardation with renal disease have been less specific. McCune,[4] discussing growth in organic disease in general, has written, "It is banal to state that any morbid process which interferes with important physiological processes will restrict growth not of the bones alone but of the soft parts as well." Watson and Lowrey [2] state that chronic renal insufficiency of severe degree may impair growth, since "the retention of abnormal metabolites and the usual accompanying acidosis so change the internal environment that optimal cellular function is impossible." In general, then, it is implied that impaired function of an important organ system and alteration in cellular environment lead to retardation of cellular metabolism and growth failure.

In addition, several other possible causes of growth retardation in renal disease in the absence of renal rickets can be named. Chronic infection, as occurs frequently in anomalies of the urinary tract, might contribute to the growth failure, although, as will be pointed out later, infection of this type seems to have no important long-term effect on growth. Another possible factor is

Submitted for publication Jan. 5, 1956.

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This investigation was supported in part by a research grant (H-1638) from the National Heart Institute of the National Institutes of Health, United States Health Service.

* References 1 and 2.

poor caloric intake brought about by the anorexia frequently accompanying chronic illness or by the gastrointestinal manifestations associated with obstructive uropathy. Contributing to a negative caloric balance would be the loss of large amounts of protein in the urine, as occurs in nephrosis.†

Changes in hormonal balance may likewise play a role. It has been suggested [7] that inadequate caloric intake causes stunting of growth by producing a physiological hypopituitarism with decreased rate of growth-hormone production. Selye [8] has proposed that in adaptation to disease in general there is a shift in hypophyseal hormone production, with increased corticotropic hormone (ACTH) and decreased growth hormone output. These hormonal abnormalities, or perhaps some other imbalance directly produced by renal disease, should be borne in mind in considering the origin of the growth retardation.

Apart from possible hormonal abnormalities, beyond the scope of the study, the present investigation attempts to determine whether, among the diverse manifestations of renal disease, a common factor could be associated with growth failure. In general, the problem has been approached from two directions. First, the incidence of various manifestations and complications of renal insufficiency in dwarfed individuals has been determined in an effort to discover a common denominator for the stunting of growth. Second, observations have been made on the compatibility of these manifestations with normal growth. The manifestations and complications selected for study were (1) reduction of concentrating ability of the kidneys, (2) chronic acidosis, (3) failure of excretion of metabolites as manifested by persistent elevation of serum nonprotein nitrogen or urea nitrogen levels, (4) inadequate caloric intake, (5) chronic infection of the urinary tract, (6) albuminuria. The growth of children with renal rickets has also been investigated and contrasted with the growth of children with renal insufficiency but without rickets.

† References 5 and 6.

MATERIALS AND METHODS

For the study, the clinical and laboratory data for 41 patients have been reviewed. For the most part the status of renal function was determined solely from routine measurements made in the course of hospital admissions and visits to the outpatient clinic and to the office of the private physician. Few specific renal function tests were performed.

The standards for growth used from birth to the age of 5 years were from the data compiled by the Department of Child and Maternal Health of the Harvard School of Public Health. In the case of height, these data are based on recumbent length, whereas in the present study it was the general practice to use standing height beyond the age of 2 to 3 years. The discrepancy thus introduced is small compared to the deviations in height usually encountered and was therefore disregarded. The normal standards used for children over 5 years of age were those compiled from the studies of Howard V. Meredith, of the Iowa Child Welfare Research Station, the State University of Iowa.[9]

Renal concentrating ability has been assessed both by the specific gravity of daily urine specimens and by the results of the Fishberg concentration test.[10] Use of daily urines for this assessment was based on the observation that the specific gravity of urines collected at 6 or 7 a. m. is usually greater than 1.016. As an arbitrary standard, it was assumed that if 80% or more of the daily urine specimens had specific gravities less than 1.016, a concentrating defect was present. Urines collected during intravenous therapy or during a diuresis were disregarded. It should be noted that the conditions under which these urines were collected do not differ greatly from those for the Mosenthal test of renal concentrating ability.[11] By this test, the subject (adult) has a supper containing 16 oz. of fluid as well as fruit, eggs, bread, and butter; after supper no food or fluid is taken. Urine obtained the following morning is considered to be normally concentrated if the specific gravity is 1.018 or greater.

Nitrogen retention was considered to be present when the serum nonprotein nitrogen level exceeded 40 mg. per 100 ml. or when the blood urea nitrogen level exceeded 20 mg. per 100 ml.

The CO_2 content of the serum was the only criterion used for determining the presence of metabolic acidosis. Acidosis was considered to be present if serum CO_2 content was persistently below 20 mEq/liter in children up to the age of 2 years, or below 23 mEq/liter in older children.

Urinary specific gravities were measured by the usual hydrometer method or, for specimens of small volume, by the falling-drop method, using mixtures of bromobenzene and xylene.[12] No correction was made for albumin when the albuminuria was 3+ or less. For urine graded 4+ with respect to albumin, a value of 0.003 was arbitrarily subtracted from the specific gravity. Chemical methods for serum nonprotein nitrogen, blood urea nitrogen, and carbon dioxide content were those in routine use in the chemistry laboratories of the Children's Hospital and the Cincinnati General Hospital. CO_2 content was determined on serum collected under oil.

RESULTS

Types of Growth Patterns Observed in Renal Disease

Before attempting to define the factor or factors responsible for growth retardation in children with renal disease, some characteristics of growth under these conditions should be noted. In the patients studied, the patterns of retardation with respect to height fell into two broad groups: (1) complete growth arrest, and (2) children who were stunted but continued to grow at a rate equal to or slightly less than that of a child at the third percentile.

Complete Growth Arrest.—The first type of pattern, complete growth arrest, was noted in two situations: (1) in patients with renal rickets, and (2) in patients, formerly growing at a normal rate, who acquired a renal disease of a severe and fulminating type. An example of complete growth arrest with renal rickets is provided by patient J. K., a boy with polycystic disease of the kidney. His growth curve is shown in Figure 1. This boy had several acute illnesses requiring hospitalization between the ages of $4\frac{7}{12}$ years and $7\frac{5}{12}$ years, but the diagnosis of polycystic disease of the kidney was not made until the age of $7\frac{11}{12}$ years. By this time, growth in height had fallen from the 25th percentile to well below the 3d percentile. The serum N. P. N. was elevated, and urine specific gravity was low and fixed. Chronic acidosis was probably also present at this time, although determinations of serum CO_2 content and pH were not made until some months later. Mild renal rickets was present by x-ray. In the two years before death, the renal rickets and acidosis were treated with sodium citrate-citric acid therapy. The dosage was probably inadequate, inasmuch as the lesion of renal rickets did not heal and the acidosis persisted. During this two-year period, the boy showed almost complete growth arrest, gaining only 1 in. in height.

Because growth is completely arrested by renal rickets, it becomes evident, as pointed out by Park and Eliot,[13] that the degree of dwarfism with this abnormality will depend on the age of onset and its duration. The most stunted individual included in the present series (L. B., Table 1) had presumably had renal rickets for a number of years before admission. On the other hand, renal rickets was not always present when growth retardation was severe; a number of severely dwarfed children were found in whom there was no evidence of this complication.

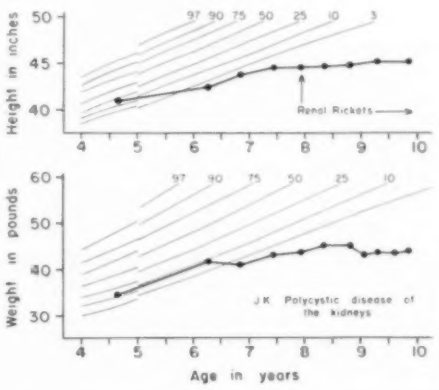
Height in inches
97 90 75 50 25 10 3
Renal Rickets
Weight in pounds
97 90 75 50 25 10
J K Polycystic disease of the kidneys
Age in years

Fig. 1.—Growth curves of J. K. Growth arrest occurred with the advent of renal rickets, complicating polycystic disease of the kidneys.

Examples of the second type of growth arrest, that is, arrest occurring after development of a severe renal lesion, are provided by patients L. K. and S. L., two little girls with nephritis with the nephrotic syndrome. Their growth curves are shown in Figure 2. L. K. developed typical signs and symptoms of nephrosis at age 24 months. Prior to this time she had been healthy, and growth had been along the 50th percentile since the age

TABLE 1.—*Data for Age, Sex, Race, and Growth for Twenty-One Patients with Renal Disease and Growth Retardation*

Patient	Diagnosis	Sex	Race	Age at Onset, Yr.	Age at Study, Yr.	Height Age, Yr.	Weight for-Height Index *
R. B.	Urethral valves; bilateral hydronephrosis	M	N	B †	4 6/12	2 11/12	1.01
J. J.	Urethral valves; bilateral hydronephrosis	M	W	B	4 9/12	3 5/12	1.05
W. S.	Urethral valves; bilateral hydronephrosis	M	W	B	3 5/12	2 7/12	0.91
R. S.	Bilateral hydronephrosis	M	W	B	2	1 1/12	0.97
J. C.	Bilateral megaloureters	M	W	B	7 9/12	4 10/12	0.92
S. M.	Nephritis; nephrotic syndrome	F	W	1 6/12	2	1 3/12	E ‡
L. M.	Nephritis; nephrotic syndrome	F	N	2	3	2 7/12	E
B. G.	Nephritis; nephrotic syndrome	M	W	3 6/12	6	5	E
J. H.	Urethral valves; bilateral hydronephrosis	M	W	B	3 10/12	2 8/12	1.02
L. K.	Nephritis; nephrotic syndrome	F	W	2	3 3/12	2 4/12	E
M. K.	Polycystic kidneys	M	W	B	6 4/12	4 2/12	1.00
K. A.	Hypoplastic kidneys	F	W	B	7 5/12	4 8/12	0.94
G. S.	Urethral valves; bilateral hydronephrosis	M	W	B	1	5/12	0.74
R. T.	Urethral valves; bilateral hydronephrosis	M	W	B	1	2/12	0.81
S. C.	Agenesis right kidney; left hydronephrosis	F	W	B	3 9/12	2 9/12	0.82
P. McK.	Bilateral hydronephrosis	F	W	B	1 7/12	1 2/12	0.80
M. T.	Nonfunctioning left kidney; right hydronephrosis	M	W	B	1	8/12	0.88
E. B.	Neurogenic bladder; bilateral hydronephrosis	F	W	B	8	3 6/12	0.97
G. O.	Hypoplastic kidneys	M	W	B	1	4/12	1.04
L. B.	Agenesis left kidney; hypoplastic right	M	W	B	8 10/12	2 10/12	1.15
J. K.	Polycystic kidneys	M	W	B	7 11/12	5 8/12	1.01

* See text for method of calculation and interpretation.
† B indicates birth.
‡ E indicates edematous.

of 6 months. Five months after onset, age 29 months, a mild renal acidosis developed which later became severer. At age 36 months, the concentrating ability of the kidneys was lost. The N. P. N. did not become elevated until shortly before death, at age 39 months. Growth in height ceased completely at age 30 months, approximately coincidental with the development of renal acidosis. At the time of death, height had fallen from the 50th percentile to between the 3d and 10th percentiles.

Patient S. L. differed from L. K. in that she was only at the fifth percentile in height before the advent of nephrosis, at age 2 3/12 years. Prior to that illness, she had had rather frequent episodes of asthmatic bronchitis. Three months after the onset of nephrosis, chronic acidosis was present and persisted until death. The N. P. N. remained normal and the renal concentrating function was good until a few months before death, at the age of 4 1 9/12 years. Again, coincidental with the development of acidosis, growth

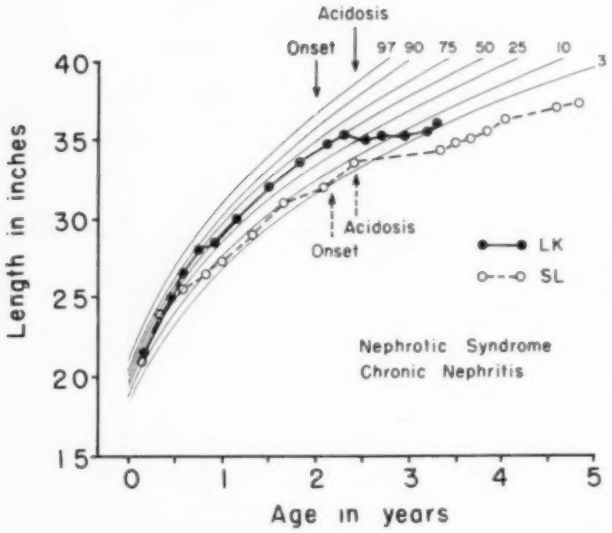

Fig. 2.—Growth curves of L. K. and S. L. Both had the nephrotic syndrome followed by chronic nephritis, with cessation of statural growth coincident with advent of acidosis. In the case of S. L., growth resumed at a lower level despite continuing acidosis.

ceased temporarily for a period of approximately six to nine months and then was resumed at a rate slightly less than that for a child at the third percentile.

Stunting with Continued Growth. — The second type of growth pattern encountered was that of children who were short in stature but continued to grow slowly at a rate approximately comparable to that of a child following the third percentile. By far the majority of patients included in the present study fall into this category. Presumably, in these patients, the renal lesion was stabilized and they had become adapted to the abnormality. An example of this pattern of growth is seen in patient S. L., the child with nephritis and the nephrotic syndrome (Fig. 2) described above. From the age of $3\frac{1}{12}$ years until death, at $4\frac{11}{12}$ years, height was below the third percentile but the line of growth approximately paralleled the third percentile. Height below the third percentile, but a slow rate of growth, was also commonly observed in children with bilateral hydronephrosis. It appeared that this type of growth would continue until the illness became terminal or renal rickets supervened.

Low Caloric Intake, Acidosis, Azotemia, and Isosthenuria as Causes of Growth Retardation

Of the many manifestations and complications of renal disease, the factors which seemed most likely to be associated with growth retardation were acidosis, inadequate caloric intake, retention of metabolites, and reduced renal concentrating ability. The relative incidence of these factors, together with other data for 21 children with renal disease and retarded growth, are shown in Tables 1 and 2. Table 1 shows the age of onset, age at study, height age, and the weight-for-height index. The weight-for-height index was determined by dividing the patient's actual weight by the ideal weight 50th percentile weight) for his height age. The index serves to measure deviations of mass growth from linear growth. Arbitrarily, an index value below 0.95 has been taken as evidence that the child has had a poor caloric intake. In Table 2 the incidence of the various manifestations in the 21 patients are recorded. All patients had had renal disease for one year or longer and were below the 10th percentile in height. Children who were known to be at or below the 10th percentile before the onset of the disease have not been included.

TABLE 2.—*Incidence of Low Caloric Intake, Reduced Renal Concentrating Ability, Acidosis, Azotemia, and Renal Rickets in Twenty-One Growth-Retarded Children* *

Patient	Diagnosis	Hypocaloric †	Reduced Renal Concentrating Ability	Acidosis	Azotemia	Renal Rickets
R. B.	Urethral valves; bilateral hydronephrosis	..	X	..	..	..
J. J.	Urethral valves; bilateral hydronephrosis	..	X	..	..	..
W. S.	Urethral valves; bilateral hydronephrosis	X	X	..	..	..
R. S.	Bilateral hydronephrosis	..	X	..	X	..
J. C.	Bilateral megaloureters	X	X	..	X	..
S. M.	Nephritis; nephrotic syndrome	E ‡	X	X	..	..
L. M.	Nephritis; nephrotic syndrome	E	X	X	X	..
B. G.	Nephritis; nephrotic syndrome	E	X	X	X	..
J. H.	Urethral valves; bilateral hydronephrosis	..	X	X	X	..
L. K.	Nephritis; nephrotic syndrome	E	X	X	X	..
M. K.	Polycystic kidneys	..	X	X	X	..
K. A.	Hypoplastic kidneys	X	X	X	X	..
G. S.	Urethral valves; bilateral hydronephrosis	X	X	X	X	..
R. T.	Urethral valves; bilateral hydronephrosis	X	X	X	X	..
S. C.	Agenesis right kidney; left hydronephrosis	X	X	X	X	..
P. McK.	Bilateral hydronephrosis	X	X	X	X	..
M. T.	Nonfunctioning left kidney; right hydronephrosis	X	X	X	X	..
E. B.	Neurogenic bladder; bilateral hydronephrosis	..	X	X	X	X
G. O.	Hypoplastic kidneys	..	X	X	X	X
L. B.	Agenesis left kidney; hypoplastic right	..	X	X	X	X
J. K.	Polycystic kidneys	..	X	X	X	X

* The presence of the abnormality is indicated by an X.
† Patients with a weight-for-height index of 0.95 or less (Table 1) are arbitrarily assumed to have had a low caloric intake.
‡ E indicates edematous.

It is apparent from the compilation in Table 2 that the only manifestation common to all patients was reduction in the concentrating ability of the kidneys. Nitrogen retention was present in 17 of the 21 cases (81%) and acidosis in 16 (76%). Renal rickets was present in only four.

The consistent occurrence of a reduced renal concentrating ability in these children is suggestive that the concentrating function is in some way related to growth. However, because the problem of growth and the mechanism of its retardation is undoubtedly complex, it seems wise, before drawing conclusions, to approach the problem from other directions.

One of the factors difficult to evaluate in the present study which could have contributed to the growth retardation is undernutrition. Insufficient caloric intake in an otherwise healthy child will produce retardation of statural growth together with diminished reserves of body fat. Probably the most reliable method to determine the presence of hypocaloric dwarfism is to observe an acceleration of statural growth when the

intake of Calories is increased.[7] Its presence can be suspected in the dwarfed child who clinically has a reduction in body fat stores or whose weight age is less than height age. It should be pointed out that assessment by comparison of height age and weight age is hazardous; children may be hypocaloric dwarfs and have low body-fat stores yet have a normal weight for height.‡ A similar criticism applies to the weight-for-height index as used in the present study. This index is derived in a manner similar to the weight age: height age ratio and is used in the present study in lieu of a better method of assessment. A value for the index of less than 0.95 has been taken as evidence that at least in part the growth retardation is the result of a poor caloric intake. Inspection of Tables 1 and 2 indicates that of the 16 patients who were not edematous and therefore allow calculation of the weight-for-height index, there are 8 whose index value was 0.95 or less and whose retardation might therefore be ascribed, at least in part, to a poor caloric intake. It is noteworthy that a number of the patients with severe renal insufficiency, and even with renal rickets, had an index value of unity or above, indicating that renal disease in no specific way alters the relationship of growth in mass to linear growth.

Role of Chronic Acidosis.—To provide further insight into the relative growth-retarding effects of the three manifestations of renal disease given in Table 2, the problem has been approached from another direction, i. e., by determining the compatibility of the three factors with normal growth.

From the case histories studied, it would appear that chronic acidosis is not compatible with normal growth. No patient was found with chronic acidosis who was above the 10th percentile in height and growing at a normal rate. All patients who were of normal stature ceased growing for a time after the development of chronic acidosis. Examples are L. K. and S. L., described above (Fig. 2). It should be emphasized, however, that chronic acidosis does not produce permanent growth arrest as does renal rickets. As pointed out for S. L. previously, after stature had become subnormal, growth resumed, albeit at a subnormal rate, although acidosis was still present. Another example of continued growth but reduced stature in the presence of acidosis is illustrated in Fig. 3. This infant, G. O., was first hospitalized at the age of 2 months because of failure to gain weight. A diagnosis of absent left kidney and hydronephrotic right kidney

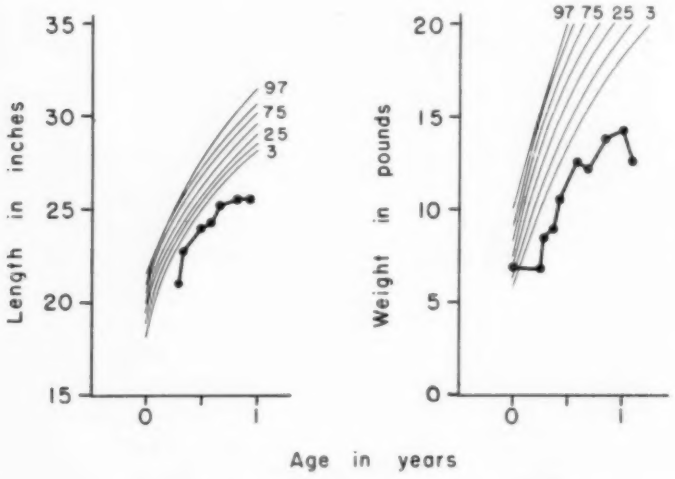

Fig. 3.—Growth curves for G. O., an infant with chronic renal acidosis.

‡ References 7, 14, and 15.

was made. Laboratory studies indicated a severe renal insufficiency, with an N. P. N. level of 120 mg. per 100 ml., a CO_2 content of 3.1 mEq/liter, and a serum phosphorus concentration of 8.3 mg. per 100 ml. In the following 12 months he was treated with sodium citrate, vitamin D, an aluminum hydroxide preparation (Amphojel), and calcium gluconate. Despite the alkali therapy, serum CO_2 content was seldom normal; of six determinations made at intervals while he was an outpatient, the highest value obtained was 15.6 mM/liter. The acidosis was, however, well compensated in that serum pH was usually 7.35 or greater. The serum N. P. N. and phosphorus levels remained elevated. X-rays of the long bones at the age of 2 months and at 8 months revealed demineralization. Renal rickets became evident one month before death. Throughout his life, the infant was below the third percentile in both height and weight. Nevertheless, in the face of the chemical abnormalities in the serum, growth did occur. In fact, rate of growth from age 3 months to age 8 months did not differ greatly from that for a child at the third percentile.

From the above observations, it would appear that the development of acidosis in a child of normal stature will slow or stop growth until stature becomes subnormal. Following the period of growth arrest, growth may be resumed at a low rate. It would appear that the body can become adapted to this abnormality.

Retention of Metabolites.—Unlike acidosis, evidence was found that retention of metabolites, manifested by elevation of the N. P. N., was compatible with normal growth. The evidence consisted of observations on two patients who were above the 10th percentile in stature and continued to grow at a normal rate although the clearance of metabolites by the kidney appeared to be defective. The best example is M. J., a Negro girl, who, at the age of 9½ years, had scarlet fever followed in one month by acute nephritis manifested by severe hypertension, convulsions, edema, hematuria, and albuminuria. These signs and symptoms subsided with treatment, but elevation of B. U. N. and N. P. N. persisted. On 18 occasions during the following four and one-half years, the B. U. N. was found to vary between 19 and 30 mg. per 100 ml. (average 24 mg.) and the N. P. N. between 37 and 51 mg. per 100 ml. (average, 44 mg.). The urea clearance ranged between 45% and 66% of normal. At no time was there evidence of defective renal concentrating ability or of acidosis. Despite the retention of metabolites, it may be seen in Figure 4 that height rose from the 10th to the 25th percentile at

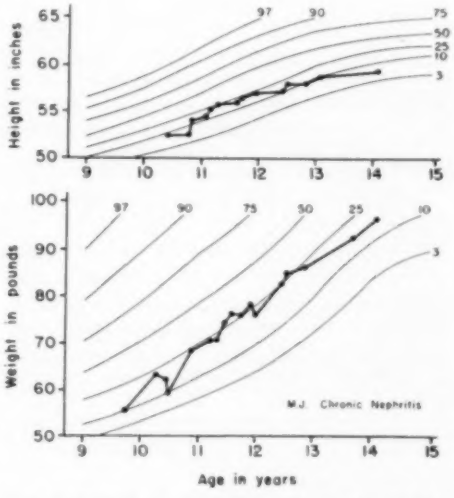

Fig. 4.—Growth curves of M. J., a Negro girl. Following acute nephritis at age 9½ years, mild, chronic renal insufficiency developed, manifested only by azotemia and reduced urea clearance.

age 11 years, one and one-half years after the initial episode, later falling off with onset of puberty to slightly less than the 10th percentile. Over this period weight remained close to the 25th percentile. While the adolescent growth spurt of this girl was not optimal, it is apparent that in the years prior to onset of puberty, growth was little affected by the azotemia.

The pattern of growth in the second patient, H. K., is shown in Figure 5. This boy had onset of the nephrotic syndrome at the

age of 6 years and remained edematous to a variable degree for the next two and one-half years. Evidence of defective clearance of metabolites by the kidney was present from the start. The initial B. U. N. level was 41 mg. per 100 ml., and, over the next two years, values between 19.5 and 39.4 mg. per 100 ml. were obtained. Two years and ten months after onset of symptoms, age 8 $10\frac{1}{12}$ years, edema was no longer a problem, although mild puffiness of the eyes was noted at intervals for the next six years. There was little apparent improvement in the clearance of metabolites, however. At age 10 $\frac{7}{12}$

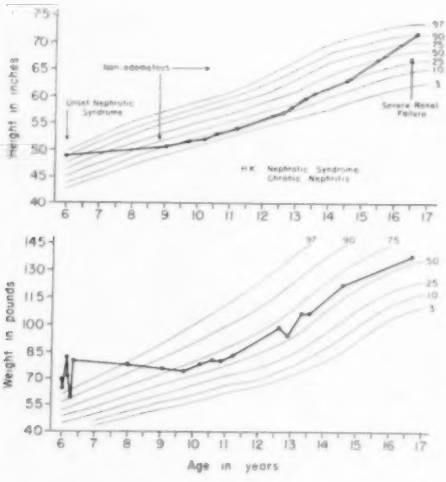

Fig. 5.—Growth curves on H. K., a boy who developed chronic nephritis following the nephrotic syndrome. Despite continuous azotemia, growth spurt occurred between the ages of 13 and 16 years.

years, the urea clearance was 53% and the B. U. N., 22.5 mg. per 100 ml. One month later the N. P. N. was 45 mg. per 100 ml. and urea clearance 41% of normal. At this time height was at the 6th percentile, having dropped to this level from the 90th at the onset of illness at age 6 years. In succeeding years no studies of kidney function were made. It seems reasonable to assume, however, that elevation of B. U. N. and N. P. N. continued. At the age of $16\frac{1}{2}$ years the boy was admitted in extremis, with severe renal failure. Symptoms of easy fatigability and mild edema had been present for the previous six to eight months. At autopsy the kidneys were small and contracted, each weighing 55 gm. Despite the renal insufficiency a growth spurt occurred from ages 13 to $16\frac{1}{2}$ years, height increasing from the 10th percentile to the 90th percentile. This growth spurt apparently occurred at a time when at least a mild and perhaps a marked retention of metabolites was present.

Reduced Renal Concentrating Ability.—Although Table 2 indicated that reduced concentrating ability was present in all cases of growth retardation, the importance of this factor is lessened by evidence that reduced concentrating ability could be present in children growing normally. The evidence consisted of two patients, one, a boy with nephrosis who has subsequently completely recovered and the other, a boy with infravesical urinary tract obstruction and with mild hydronephrosis. In neither case were specific tests of concentrating ability carried out, the defect being detected from the specific gravities of routine specimens.

R. R. was a Negro boy who had onset of symptoms of nephrosis at $4\frac{1}{2}$ years. The growth curve, shown in Figure 6, starts at age of 5 $\frac{4}{12}$ years, when he was first admitted to the Children's Hospital. At this time, the serum N. P. N. level was not elevated, blood pressure was normal, and acidosis was not present. In the course of five admissions over a period of two years two months, the N. P. N. level was found to be occasionally elevated, but there was no evidence of acidosis, hematuria, or hypertension. The specific gravity of the urine was, on the other hand, consistently low. Of 97 specimens obtained at times when weight was stable, only 14 had a specific gravity over 1.016. Throughout the period of illness, height remained between the 25th and 50th percentiles. Recovery from the disease was apparently complete, and the boy is now in good health.

The second patient, L. O'N., a boy, first seen at the age of 8 $\frac{3}{12}$ years, had been in good health until an acute urinary tract in-

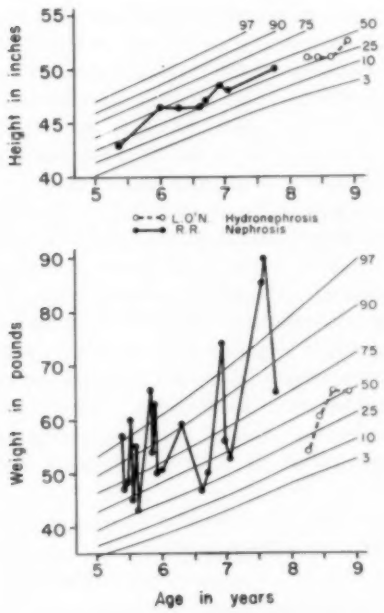

Fig. 6.—Growth curves of R. R., a Negro boy with the nephrotic syndrome, and L. O'N., a boy with hydronephrosis resulting from infravesical obstruction. Both showed normal height growth despite inability to concentrate the urine.

fection caused the parents to seek medical attention. Studies revealed enlarged kidneys, with bilateral hydronephrosis and hydroureter of mild degree. The obstruction was felt to be the result of either hypertrophy of the verumontanum or a neurogenic bladder. Serum N. P. N. levels ranged between 48 and 58 mg. per 100 ml., but acidosis was not present. Of 24 morning urine specimens examined, none had a specific gravity greater than 1.010. The duration of the hydronephrosis and the concentration defect could not be ascertained from the history; the boy had never had urgency, dysuria, frequency, or enuresis. It may be seen in Figure 6 that, despite the hydronephrosis and failure to concentrate the urine, the boy was normal in weight and height and during the year of observation had a normal rate of growth.

It must be concluded from these observations that reduction in renal concentrating ability, although found with high frequency in children with growth retardation, is nevertheless compatible with normal growth.

Albuminuria and Chronic Urinary Tract Infection as Factors in Growth Retardation

Remaining as possible factors in the growth retardation of renal disease are albuminuria and chronic urinary tract infection. There is considerable evidence that neither of these factors significantly affects growth. The effect of massive albuminuria on growth is best assessed by the study of the growth of children with pure lipid nephrosis. It would appear that pure nephrosis, in contrast to the nephrotic stage of chronic glomerulonephritis, does not necessarily interfere with growth. Block and co-workers,[16] in a study of 40 children with nephrosis, present growth data for 3, none of whom showed interruption of statural growth during the disease. They state that "growth and development were uniformly good, even of children with many and severe exacerbations." From growth data for children with pure nephrosis accumulated in the course of the present study, it would also appear that even long-continued massive albuminuria has indeed little effect in inhibiting growth.

The contribution of chronic urinary tract infection to growth is of some importance in the present study, since many of the children investigated had the chronic infection of the urinary tract which is inevitable when nephrostomy tubes and suprapubic and urethral catheters are left in place over long periods of time. Insight into the possible effect of this type of infection on growth can be gained by experience with the effect of chronic infection in other parts of the body.

The chronic infections most usually associated with growth retardation[17] are (1) those accompanied by an abnormality in function of the gastrointestinal tract, such as abdominal tuberculosis, intestinal parasitism, or chronic dysentery, (2) those producing abnormality in the growing ends of the bone, as in congenital syphilis, (3) severe systemic disease, such as malaria, and perhaps also

(4) infections producing extensive necrosis and tissue breakdown, as in severe chronic osteomyelitis. Localized chronic infection with a specific organism does not appear to retard growth. Reynolds and Sontag [18] report a child ill 42 months with primary pulmonary tuberculosis who showed no lag in growth. Likewise, localized nonspecific infection seems to have relatively little effect on growth. Evans,[19] in a study of preschool children, found that children who were repeatedly ill with such diseases as pneumonia, bronchitis, tonsillitis, and severe mumps, necessitating prolonged absence from school, grew as well as those who had perfect school attendance. Similar observations had been made previously by Hardy,[20] Palmer,[21] and Martens and Meredith.[22]

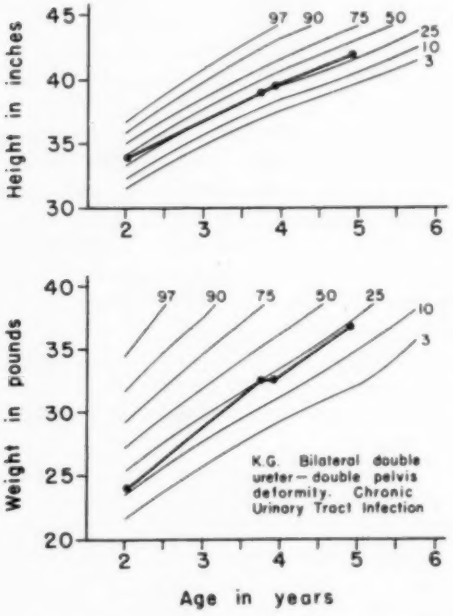

Fig. 7.—Growth curves of K. G., a girl with chronic urinary tract infection as a result of a renal anomaly. The presence of infection appeared to have no influence on the rate of growth.

Evidence that chronic infection localized in the urinary tract does not retard growth was provided by K. G., a girl with a double ureter, double pelvis deformity. Her growth curve is shown in Figure 7. After a right heminephrectomy, performed at the age of 2 years, considerable residual hydronephrosis was still present on the right and mild hydronephrosis on the left. From the age of 1 $^{11}/_{12}$ years to 6$^{1}/_{12}$ years she had frequent acute exacerbations of chronic urinary tract infection which were intermittently treated with chemotherapeutic drugs and antibiotics. The infection was probably never completely eliminated. All urine specimens showed evidence of infection, with white cells and the presence of organisms on culture. Despite the continuing infection there was no evidence of renal insufficiency. Over a four-year period, height and weight remained constantly at the 25th percentile.

COMMENT

None of the factors in the present study emerges as a distinct common denominator for the growth failure of renal disease. The significance of reduction of urinary concentrating ability, demonstrated as present in every patient with growth retardation, is diminished by the fact that it was observed in a few patients growing normally. On the other hand, chronic acidosis was present in only 76% of the stunted patients but was never observed in children growing normally. Retention of metabolites, at least of mild degree, appears to have little or no effect on growth.

Further light can be thrown on the problem by speculation as to the effects of these abnormalities on the organism and the mechanism by which they might influence growth. In the case of diminished renal concentrating ability, the only effect on the organism, so far as is known, would be the requirement for a greater rate of water turnover. Assuming the amount of total solute requiring excretion to be in the normal range, failure to concentrate the solutes would require the excretion of a greater urine volume and hence demand a greater water intake. From observations on patients with diabetes insipidus studied before pituitary hormone preparations were available, it would appear that

accelerated water exchange lasting throughout life is without effect on growth. The Weils § have described 58 individuals in one family afflicted with diabetes insipidus from an early age, yet they were normal in all other respects. Dismissing accelerated water turnover as a cause of growth failure, growth failure and failure to concentrate may be linked by assuming that some substance essential for normal growth, he nature of which is not as yet known, is lost by excretion and that the tubular mechanism for conserving this substance is closely related in morphological site or in function to that for the reabsorption of water. Thus, renal damage sufficient to cause loss of water-conserving ability would be associated with high frequency with excessive excretion of "growth" substance and hence to growth failure. Such a causal relationship is, of course, only speculative.

On the other hand, chronic acidosis would upset the economy of the organism in a number of ways. In addition to causing a change in the reaction of the fluids bathing the cells, it would also presumably alter the distribution and amount of electrolyte in the body. In experimental animals, acidosis, induced by the depletion of body sodium and maintained by a low sodium diet, results in an increase in the potassium and water content of muscle cells and a decrease in muscle-cell sodium content.‖ Whether comparable changes occur in renal acidosis and, if so, whether they would interfere with cell multiplication has not been determined. In addition, failure to acidify the urine could result in a reduction in the body content of sodium, potassium, and calcium. All of these ions are necessary for normal growth. Of the three, depletion of body calcium would appear most liable to occur in chronic acidosis. Depletion would result from loss in the urine and also, perhaps, absorption of ingested calcium might be less in acidotic than in normal individuals. Gastric acidity, an important factor in calcium absorption, has been described as reduced in acidosis.[26] That adequate calcium intake is necessary for normal growth has been well established.[27] However, it should be remembered that experimental animals reared on diets varying in calcium content may have considerable differences in body composition with respect to calcium but exhibit only small differences in their rates of growth.¶ It would appear that calcium loss would have to be considerable to produce significant slowing in the rate of growth. In considering the possible effects of acidosis on growth, it should be borne in mind that according to the present study chronic acidosis does not totally prevent growth. In several patients, chronic acidosis appeared to cause temporary growth arrest, but, once stunted, the acidotic individual continued to grow at a slow rate.

The conclusion that retention of metabolites of mild degree does not interfere with growth also seems reasonable. It is well known that urea, the metabolite whose concentration shows the greatest elevation under these conditions, is a relatively benign substance well tolerated by the body. Whether severe azotemia with elevation of other metabolites to significant levels would interfere with growth cannot be determined. Persistent, marked azotemia without acidosis or other complications is seldom encountered.

Endocrine Factors.—The present study by no means rules out changes in the endocrine influences on growth as the fundamental factor causing the retardation in these children. Too little is as yet known about hormonal control of growth to determine in a study such as this the extent of the derangement of the endocrine system or to define the effect of such derangement in producing retardation. It is now fairly well established that, with the exception of the temporary effect of testosterone, pituitary growth hormone is the endocrine product primarily concerned in growth. A number of factors are known to influence the rate of production and/or the end-organ response to this hormone. For

§ Weil, A., and Weil, A., cited by Warkany and Mitchell.[23]

‖ References 24 and 25.

¶ References 28 and 29.

example, the adrenal 11-oxycorticosteroids, either when given directly or when produced in excess by the body as the result of corticotropin administration or of Cushing's syndrome, will inhibit the end-organ response of the skeletal system to the pituitary growth hormone.# Similarly, estrogenic hormone stops growth apparently by inhibiting pituitary growth hormone production rather than by interfering with the end-organ response.[35] It has been suggested[7] that poor caloric intake, by producing a physiologic hypopituitarism,[36] likewise decreases the rate of growth hormone production. Experimental animals given a diet low in Calories will grow if given growth hormone, provided certain essential elements are present in the diet.[37] Thus the endocrine system may be, in part, responsible for growth retardation in undernourished children, and until proved otherwise it could be conjectured that chronic acidosis or some other more subtle abnormality resulting from renal disease also affects growth by a derangement in endocrine balance rather than by a direct effect on cell metabolism. The concept of a shift in hypophyseal function in the general alarm reaction with consequent diminished growth hormone and increased corticotropin and adrenal steroid production, as described by Selye,[8] may explain the temporary growth retardation accompanying acute disease but seems unlikely to account for the gross retardation seen with chronic renal disease.

Multiple Factors.—Failure to demonstrate conclusively that a single factor is responsible for the growth retardation of the patients examined leads to the possibility that multiple factors are operative. The most important of the several factors evaluated would appear to be chronic acidosis and lack of sufficient Calories. Chronic acidosis appears to have a clear-cut growth-retarding effect and could account for the retardation of 16 of the 21 patients. Of the five remaining, two can be considered hypocaloric dwarfs according to assessment by weight-for-height index (Table 2). Thus the retardation of 18 patients could be accounted for. Further investigation of the three nonacidotic patients whose retardation is not accounted for fails to reveal a cause for the retardation of one but suggests that the other two may have been hypocaloric dwarfs at the date of study. Both of these children (R. B. and J. J.) had severe bilateral hydronephrosis with only reduction of urinary concentrating ability as their manifestation of renal disease. Surgery to institute adequate urinary drainage was performed at the age of $3\frac{1}{12}$ years on R. B. and $4\frac{9}{12}$ years on J. J. Following surgery their appetites were noted to improve, and, as can be seen in Figure 8, their rates of growth began slowly to accelerate. By the age of 7 years, R. B. had progressed from marked dwarfism to the 3d percentile in height and to the 10th percentile in weight.

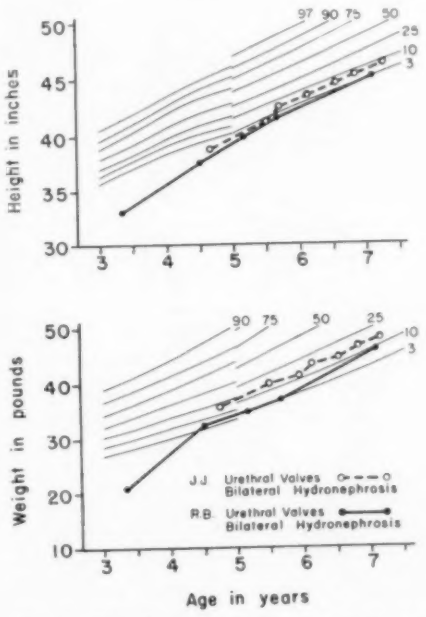

Fig. 8.—Growth curves of J. J. and R. B., both boys with infravesical obstruction and hydronephrosis. Surgery to institute drainage, performed at age $3\frac{1}{12}$ on R. B. and age $4\frac{9}{12}$ on J. J., was followed by a slight (J. J.) to marked (R. B.) acceleration in growth, although renal function was little altered.

References 30-34.

These accelerations in growth occurred in the absence of apparent change in the severity of the hydronephrosis or in renal function. It seems reasonable to assume that the initial growth retardation in both of these children was the result, in large part, of an inadequate caloric intake, although their initial weight-for-height indices were normal. The combined factors of acidosis and inadequate caloric intake would then account for the retardation of 20 of the 21 patients in the present series.

does not appear to be a consequence of acidosis; several of the acidotic children showed no evidence of poor food intake, judging by their weight-for-height indices. Finally, two endocrine abnormalities have been included as possibly responsible for growth retardation, one, a loss of a "growth substance" in the urine in association with hyposthenuria, and the other, a direct effect of renal disease on that part of the endocrine system responsible for growth. These mechanisms would be of major importance if their existence could be proved.

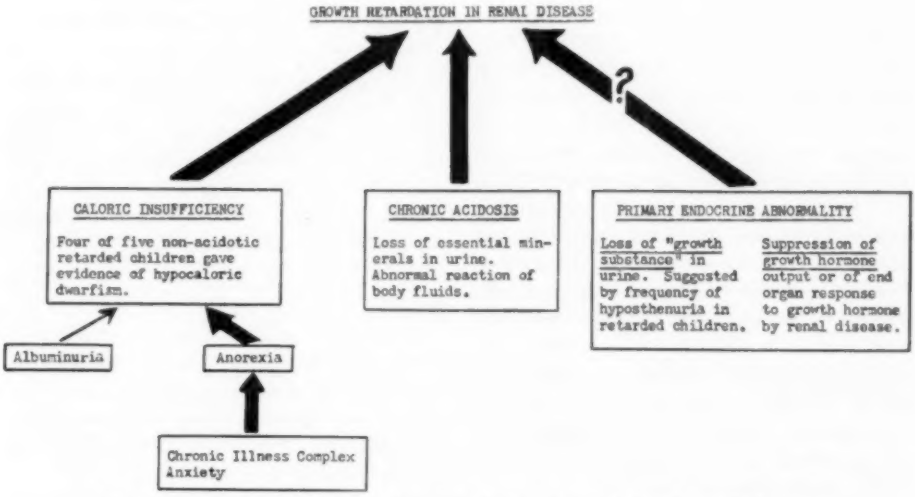
GROWTH RETARDATION IN RENAL DISEASE
?
CALORIC INSUFFICIENCY
Four of five non-acidotic retarded children gave evidence of hypocaloric dwarfism.
CHRONIC ACIDOSIS
Loss of essential minerals in urine.
Abnormal reaction of body fluids.
PRIMARY ENDOCRINE ABNORMALITY
Loss of "growth substance" in urine. Suggested by frequency of hyposthenuria in retarded children.
Suppression of growth hormone output or of end organ response to growth hormone by renal disease.
Albuminuria
Anorexia
Chronic Illness Complex
Anxiety

Fig. 9.—Graphic representation of causes of growth retardation in renal disease.

In an attempt to clarify the causes of growth retardation, the various factors involved have been graphically represented in Figure 9. Chronic acidosis and lack of sufficient Calories are represented as the most important of the known factors responsible. Hypocaloricism is represented as arising to a slight extent from albuminuria but mainly from anorexia. For the purposes of this discussion, anorexia is defined as a loss of appetite resulting in a sufficient diminution of food intake to keep body weight below the normal for height age. The origin of the anorexia is ill-defined; anxiety and the psychic effects and debilitation produced by chronic illness are possible factors. Anorexia

Reduced Renal Concentrating Ability.—The observation that a defect in renal concentrating ability was present in every case of renal disease with growth retardation points to the diagnostic importance of the examination of this renal function in cases of dwarfism or of suspected renal disease. It is noteworthy that in the majority of cases, concentrating ability can be fairly accurately judged by the specific gravity of several routine morning urine specimens without resorting to special preparation of the patient for a concentration test. In cases in which routine specimens show low values, a simple concentration test, such as that described by Fishberg,[10] may be done. With specimens of

small volume as frequently obtained in infants, the falling-drop method for urinary specific gravity,[12] requiring only a fraction of a cubic centimeter of urine, has been found equal in value to the hydrometer method. Installing the falling-drop procedure as an alternate to the hydrometer method in the routine laboratory avoids the frustration of frequent reports of "quantity not sufficient."

A few comments are in order concerning the origin of the concentrating defect in these children. The studies of Platt [38] have given evidence that in renal damage of the type seen in chronic nephritis in which there is widespread destruction of whole nephron units with the remaining functioning nephrons hypertrophied the failure to concentrate the urine can be ascribed to an increased rate of solute excretion per nephron. In these patients the daily rate of solute excretion is approximately the same as in the normal subject, but because of the paucity of functioning nephrons and the consequent azotemia, solute excretion per nephron is increased to rates comparable to that of a normal individual undergoing solute diuresis. Since solute diuresis in normal subjects always results in a lowering of urinary concentration,* the concentration defect in these patients can be explained without invoking malfunction of the remaining specific tubular cells involved in the reabsorption of water.

On the other hand, the solute diuresis-per-nephron concept does not explain the origin of all concentrating defects. In many of the patients in the present study who failed to concentrate, hydronephrosis was present with little or no elevation of the N. P. N. or B. U. N. One can assume that in these individuals most of the nephron units were functioning but that all were to some extent damaged by the back pressure of urine. Rates of solute excretion per nephron can thus be assumed to have been normal, and failure to concentrate must be ascribed to damage of the specific tubular cells involved in the reabsorption of water. Since the concentrating function supposedly resides in the distal portion of nephron, failure of the concentrating function would be predicted to be an early consequence of hydronephrosis.

* References 39 and 40.

SUMMARY

In an effort to determine a common denominator for the growth failure of renal disease, the clinical and laboratory observations on 41 children with chronic renal disorders have been surveyed. Twenty-one of the patients had growth retardation. Of the manifestations investigated, none met the criterion of being universally present in the stunted patients and absent in children growing normally. Failure of renal concentrating ability was present in all children with growth failure, but failure of concentration was also observed in a few children growing normally. On the other hand, chronic acidosis was never observed in children growing normally but was present in only 76% of the retarded children. There was no evidence that mild azotemia, albuminuria, or chronic urinary tract infection significantly affected growth.

The advent of chronic acidosis in a patient with renal disease appeared to cause stunting by producing temporary growth arrest. After stature had become subnormal, growth was resumed at a slow rate, although acidosis continued to be present.

The role of low caloric intake resulting from anorexia as a cause of growth retardation in renal disease can only be assessed roughly in the present study by the weight-for-height index. According to this assessment only eight of the retarded children fall into the category of hypocaloric dwarfs. Two other children demonstrated a growth spurt after establishment of adequate urinary drainage by surgery, indicating that their dwarfism might also have been a result of low caloric intake. It was found that between the two factors of low caloric intake, as assessed by the above methods, and chronic acidosis, the growth retardation of nearly all the patients in the present series could be accounted for.

Many physicians of the Cincinnati area aided in this study by providing data from their files.

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News and Comment

ANNOUNCEMENTS

Convention of The Intermountain Pediatric Society.—The Intermountain Pediatric Society will hold its annual convention in Sun Valley, Idaho, June 7, 8, and 9, 1956. For further information write The Intermountain Pediatric Society, 2000 South 1300 East, Salt Lake City.

Post-Graduate Medical Seminar Cruise.—Duke University School of Medicine will sponsor a second Post-Graduate Medical Seminar Cruise on Oct. 27, 1956. Sailing on the S. S. Nassau, the cruise will take 18 days from New York and will constitute 25 hours of formal teaching. The ship will visit Madeira, Casablanca, Cadiz, Palermo, Naples, and Rome. The Faculty will consist of Dr. Wilburt C. Davidson, Professor of Pediatrics and Dean of the School of Medicine; Dr. William McNeal Nicholson, Professor of Medicine and Director of Post-Graduate Education; Dr. Lenox D. Baker, Professor of Orthopaedic Surgery; Dr. Leslie B. Hohman, Professor of Psychiatry; and Dr. Edward S. Orgain, Professor of Medicine. Further information may be obtained from the Director of Post-Graduate Education, Duke University School of Medicine, Durham, N. C.

Meeting of Canadian Paediatric Society.—The Canadian Paediatric Society will meet at Delawana Inn, Honey Harbour, on Georgian Bay, on June 4, 5, and 6, 1956. President, J. Harry Ebbs; Secretary-Treasurer, J. C. Rathbun.

Tuberculous Meningitis in Children

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The present study is the report on 134 treated cases of proved tuberculous meningitis, treated at the Hospital for Sick Children, Toronto, Canada, in the eight and a half years since streptomycin became available. In addition, there were 17 cases of abacterial lymphocytic meningitis in tuberculous children. Eight others were admitted to the hospital moribund and died within 24 hours, before therapy could be effective; therefore, these cases are not included. The alterations made possible in the prognosis with streptomycin and later chemotherapeutic drugs in a disease so mortal that its diagnosis signified imminent death have been most gratifying. During this period not only has there been a steady decline in mortality, but the survivors have been left with progressively fewer sequelae.

There are three types of tuberculous meningitis. First, 70% of all cases are primary infections of the cerebral meninges, but hematogenous spread. The latter may be a sudden heavy seeding from a massive dose, or rupture of a tubercle, caused in the past by deposition of a few organisms from the blood stream. In these cases bacteriological proof of acid-fast infection was always present in the spinal fluid, either by smear, culture, or animal inoculation, and usually in all three. In the second group (17 cases) bacteriological proof of the disease was not found. They presented the picture of abacterial serous meningitis in children described by Lincoln and Kirmse.[1] These are not included as tuberculous meningitis in the reports of this disease in this study. Their disease, however, appears to be of more serious import than a serous meningitis, in that three patients developed serious complications, two had hydrocephalus and deafness, and another became completely deaf. Nine made a complete recovery. One died. It appears probable that such findings in a child at the present time might be diagnosed as tuberculous meningitis, with a negative culture because of drug therapy for disease elsewhere, or early diagnosis when lumbar punctures are done in potential cases before symptoms and signs of meningeal involvement are found.

The third, and very important, group comprises those cases in which primary spinal cord infection is present. Such persons may or may not have Pott's disease. They constituted 17% (23 cases) of the entire group. These cases present major problems in treatment because of spinal canal block. It became apparent very early that meningeal patients with Pott's disease had a high mortality rate. In 1948, six out of seven of these cases were fatal. They are readily differentiated from primary meningeal cases by both their history and laboratory findings. The duration of symptoms is usually longer, sometimes as long as six months, before meningitis is thought about. A fall often produces back pain, staggering, or clumsy gait. Abdominal pain, probably of root origin, is common and may even result in unnecessary abdominal surgery. Some cases have been wrongly diagnosed as polio. These patients develop stiff necks, while the sensorium is little affected in contradistinction to the cerebral meningeal cases. The spinal fluid may be difficult to obtain. This fluid is xantho-

Submitted for publication Oct. 24, 1955.

From the Department of Paediatrics, University of Toronto, The Research Institute of the Hospital for Sick Children, and the I. O. D. E. Hospital for Tuberculosis, Toronto, Canada. Aided by a grant from the Federal Government.

Presented at the Combined Meeting of the American Pediatric Society, British Paediatric Association, The Society for Pediatric Research, and Canadian Paediatric Society—Société Canadienne de Pédiatrie, Quebec, Canada, June 16, 1955.

TABLE 1.—*Results of Treatment*

Year	No. of Cases	Deaths		Cures			Severe Residual Damage			Treatment
		No.	Per Cent	No. of Cases	Per Cent of Survivors	Per Cent of Cases	No. of Cases	Per Cent of Survivors	Per Cent of Cases	
1947	6	5	83	0	0	0	1	100	17	Streptomycin intramuscularly and intrathecally to beginning of 1948; 6 cases
1948	17	10	59	3	17	43	3	43	19	Streptomycin intrathecally and intramuscularly plus thiazolsulfone, to middle (May) 1949; 25 cases
1949	27	9	33	6	22	33	8	44	29	May 1949, streptomycin intrathecally and intramuscularly plus P. A. S. (oral)
1950	20	6	30	7	35	50	4	29	20	Intramuscular, intrathecal streptomycin plus P. A. S., May 1950; burr holes plus intraventricular therapy with streptomycin and P. P. D.
1951	20	3	15	8	40	47	5	30	25	Same as 1950
1952	15	4	28.5	8	53	73	2	19	18	Burr holes when needed but no intraventricular therapy March 1952; intrathecal streptomycin discontinued, also P. P. D.; isoniazid oral plus streptomycin intramuscularly
1953	16	3	18	10	63	77	2	15	12.5	Same as 1952
1954	10	0	0	9	90	90	0	0	0	Same as 1952 and 1953
1955	4	0	0	All doing well to date (June/55)			0	..	..	.....
	135	40	29	51	53	38	25	27	18	

chromic. A heavy protein coagulum forms as soon as the fluid is withdrawn. Polymorphonuclears instead of lymphocytes are present early. Ventricular fluid is clear, and typical of the primary cerebral cases.

PROGNOSIS

Four major factors influence the prognosis (Table 1). The most serious of these is the delayed application of therapeutic measures because of late diagnosis. This increases both mortality and complications. All cases should be treated, since if the patients survive two to three days after initiation of therapy they may recover.

The age of the patient in the past has been a strong determinative factor. No child under 2 years was reported to have survived in the pre-streptomycin days. Many have failed to survive since, but in the period since March, 1952, when intrathecal therapy was discon-

TABLE 2.—*Results of Treatment, Tuberculous Meningitis*

Year	No. of Cases	Deaths	Complete Cures	Mild Residual Damage	Severe Residual Damage
1947	6	5 83%	0	0	1, survivor has I. Q. of 25 and is hydrocephalic
1948	17	10 59%	3 1.7%	1, spastic leg, corrected by operation, only slight limp	1, severe organic behavior problem, I. Q. 106 1, total deafness, I. Q. 60 1, total deafness, normal I. Q.
1949	27	9 33%	6 22%	2, deaf but able to attend ordinary school	1, blind, I. Q. 130 2, total mental wrecks 3, totally deaf, but normal I. Q. 1, hemiplegia, low I. Q. 1, spastic, I. Q. 60, died 4 years later, brain photo
1950	20	6 30%	7 35%	2, deaf, normal I. Q., ordinary school 1, spastic leg, corrected by surgery	2, complete mental wrecks 1, deaf, I. Q. 60 1, deaf, mildly hydrocephalic, I. Q. 70
1951	20	3 15%	8 40%	4, deaf, normal I. Q., attend school 1, spastic leg, no real disability	1, epileptic 1, complete mental wreck 1, spastic, dull normal 1, Cushing's syndrome, calcified pituitary fossa, low I. Q.
1952	15	4 28.5%	8 57%	1, slight deafness, ordinary school	1, behavior problem 1, complete mental wreck
1953	16	3 18%	10 62.5%	0	1, spastic, still improving 1, mental wreck
1954	10	0	9 90%	1, vestibular disturbance, still improving	0
1955	4	0	4, to date	0	0

tinued and isoniazid given, small babies have done extremely well.

Primary cord disease, if unrecognized, is of serious moment. If diagnosed early and the increased intracranial pressure relieved by ventricular taps until drugs have a chance to act, they do well. These too have been greatly improved by isoniazid therapy.

The type of extrameningeal (Table 2) disease is the fourth alterant. In this series massive caseation of mediastinal glands has proved the worst type rather than miliary disease, as many have reported. Also, in our experience with primary tuberculosis later giving rise to meningitis this type was the worst. No drug until isoniazid penetrated these caseous masses; the latter does, and this possibly accounts for the decrease in malignancy of this type of disease. None of our few [6] cavitary cases developed meningitis, nor did any of the bronchiectatic ones.

TREATMENT

The active treatment of the disease, to obtain optimum results, must include measures to help the host as well as drugs. The discovery of streptomycin and other potent drugs has made survival possible, but we are prone to forget the host in our zeal to destroy the parasite. The best results will be obtained only when both factors are considered.

Treatment directed to helping the host may be listed under five headings, all of which are important.

First, rest must be maintained until active treatment is being carried out (six months of streptomycin) and until lesions may be presumed to be healed. Otherwise the small child may fall and injure his brain, causing reactivation of the disease.

Second, it is important to correct electrolyte disturbance. In common with all the meningitides in children, this balance may be seriously upset and failure to correct it may prove fatal. Cheek [2] studied this aspect of our cases. In brief, the findings are a constant alkalosis as indicated by the high serum pH, an increase in bromide space suggesting an increase in extracellular fluid, and a normal NaCl in terms of amount. The K is low, which in itself accounts for the expansion of intracellular fluid. The disturbance readily adjusts itself when food can be taken, otherwise large amounts of K and Na with minimal fluid intake are indicated. Isoniazid therapy results in a much earlier ability to take food and thereby makes such corrections more rarely needed.

Third, the relief of increased intracranial pressure by mechanical means may be an emergency, if the patient is to be kept alive. This is particularly true in spinal cord cases, or in those where late diagnosis has permitted the typical basilar collar of granulation tissue to form. In this series this lifesaving relief of pressure was accomplished by doing prefrontal burr holes by craniotomy. This permitted ready access to the ventricles for the withdrawal of fluid to produce relief without jeopardizing the patient's life by producing medullary impaction. This procedure has been carried out in 40 cases. Before intrathecal therapy was discontinued, drugs and tuberculin were administered through polyethylene tubes into the ventricles. This is no longer necessary. Craniotomy now is done only to permit the reduction of intracranial pressure by withdrawal of ventricular fluid. The latter usually is necessary for only a few days.

Fourth, tuberculin has, in the past, been of great value in the treatment of the disease in association with posterior basal block. It has only been used in the so-called "vegetable" cases, where other means were proving inadequate. It was started in 1950 after hearing Dr. Cairns and Dr. Vollum speak on their work, and followed the same pattern used by Dr. Honor Smith of their group. Purified protein derivative (PPD) was used and was injected intraventricularly daily with the streptomycin. The patients had all needed craniotomy to relieve their increased intracranial pressure. Twenty-five patients were treated by this means, and ten survived. As was to be expected from the type of cases treated, complete cures were few. Five of them had residual damage of high degree, one had deafness only, and four are cured. This

type of therapy has not been needed since isoniazid became available, as this drug accomplishes the same purpose in a less barbaric fashion.

Last, certain drugs such as isoniazid have side-effects of benefit to the host. The observation that a Cushing-like syndrome often followed its use, led Boyd, Roy, and Josiukas [3] to investigate the 17-ketosteroid excretion in patients on this drug. It was found that the lowered excretion of these substances in tuberculosis was regularly increased by giving this drug. Further, withdrawal symptoms were accompanied by a sudden fall in their urinary concentration.

Drug Therapy. — Streptomycin became available to us at the end of 1946. It was given both intrathecally and orally from the start. At first a trial-and-error method was used as to dosage. By the end of 1948 a dosage pattern was established of 0.5 gm. intramuscularly twice a day and 25 mg. intrathecally daily. The mortality rate fell, and cures began to appear. Since it was recognized early that the organism lost its sensitivity to the drug, the first improvement in treatment was the addition of a second drug to the therapeutic regimen. This prolonged the sensitivity of the organism to streptomycin and had bactericidal effects itself. Thiazolsulfone (Promizole) was added at the beginning of 1948. This was given orally. It produced a good effect. Tolerance to it was good in most patients, but vomiting or anorexia was sometimes caused. It was replaced by oral aminosalicylic acid (PAS) in September, 1949. This drug was well tolerated. A few developed rashes severe enough to force discontinuing its use. It was used regularly until March, 1952, when isoniazid became available. It has not been used in the meningeal cases since, with one exception, a child who appeared moribund on admission, and it was believed that all the ammunition was needed. It was only given during the first three weeks of treatment.

Intrathecal administration was discontinued entirely after isoniazid became available. Our own studies and those of others [5] showed that in meningeal cases effective concentrations of the drug could be reached and maintained in the cerebrospinal fluid. Others [6] thought the need for it unconvincing. Lumbar taps or, in those in which craniotomy was needed, ventricular taps have been done to relieve pressure. This necessity usually lasts only the first two to three weeks of illness. It is done daily at first, then with decreasing frequency as the manometer pressure falls, or free flow of fluid by lumbar tap occurs. Subsequently, taps are only done to follow the progress of the disease. The lumbar route is adequate very early even in those who at first needed craniotomy because of block.

Treatment since March, 1952, consists of the following:

Streptomycin 0.5 gm. is given twice a day intramuscularly for three months, then every second or third day to six months.

Isoniazid 10 mg. per kilogram of body weight is given daily, orally, in two doses 12 hours apart. This is reduced to 5 mg. at the end of three months, and to 2.5 mg. per kilogram of body weight daily in six to nine months, depending on the progress of the disease. It is continued at this dose for one to one and one-half years.

Craniotomy is done in cases with high intracranial pressure, whether due to cord block or a basilar collar of granulations. Ventricular fluid is aspirated daily until the pressure is relieved, at most 7 to 10 days.

Since this regimen was adopted, there have been no deaths and no complications in 40 cases other than slight squint (three cases) and one transitory vestibular disturbance.

RESULTS

Cause of Death.—(1) The Disease Itself: Deaths from the disease itself would be the inevitable fatal outcome of untreated cases. This would occur now in those patients whose organism was completely insensitive to any of the drugs, or where they were not given in an adequate manner. In only one of our cases were all effects of the drug nullified by lack of sensitivity. Unwise or too short administration of drugs was doubtless responsible for some deaths in 1947. Deaths also oc-

curred in the early years because of failure to relieve the high intracranial pressure and failure to recognize and rectify electrolyte imbalance.

(2) Recurrences: Three children died of recurrences shortly after apparent cure. In the first, the exacerbation was doubtless due to too early withdrawal of therapy. The child presented a picture of cure at the end of two months' treatment. This was carried on another month and then stopped. Two months later she had the full-blown picture of acute meningitis, which proved fatal in a week despite resumption of streptomycin therapy. The organism obtained at autopsy was completely insensitive to streptomycin. The postmortem examination revealed a typical picture of tuberculous meningitis. This was before the days when a second drug prolonged the sensitivity of the organism to streptomycin. The second recurrence shortly after a seemingly good recovery resulted when a fall caused a fractured skull. It occurred 12 months after treatment was started, and 6 months after its discontinuance. Here again, despite the previous use of PAS with the streptomycin, the organism had become insensitive, and therapy was ineffectual. The third child died in convulsions a short time after active treatment was stopped. No autopsy was permitted, and her spinal fluid was negative; therefore the sensitivity of the organism and the cause of death are unknown.

Three other children died with recurrences three to four years after the original illness. One had been treated elsewhere as a newborn, who developed his disease from a nurse in the nursery. The treatment was apparently successful, but was stopped at the end of three months. The child was then well for four years, during which time he was apparently a perfectly normal child. After a febrile illness of three weeks mild meningeal symptoms developed. Because his cerebrospinal pressure was very high, burr holes were made and ventricular drainage was done. Tubercle bacilli were cultured from the spinal fluid. A subdural hematoma caused his death. Little evidence of meningitis was found at autopsy. A second child survived for four years after the initial attack. She was defective mentally and had a left hemiplegia. The child was examined at the clinic and found to be in good condition, for her. The day after this she was vaccinated. Ten days later, concurrent with the take, meningeal symptoms developed, and she died three days later. The vaccination evidently acted as a trigger to flare up the tuberculous disease. The acute changes in the brain could have been due to vaccinal encephalitis. The photograph showed the residual severe damage from the previous meningitis. Tubercle bacilli were cultured from these lesions and produced disease in the guinea pig. The third patient who lived for three years after the initial attack died suddenly with hemiplegia, rapidly succeeded by unconsciousness. No autopsy was permitted. She also had syphilis, and it was impossible to discover which of her diseases was responsible for her death.

(3) Severe Cord Lesions: Two patients had sufficiently severe myelitis to cause death even without the cerebral lesions. When streptomycin was the only drug used and tuberculin not yet considered, five out of six with severe cord damage died. Cord changes are the cause of the block to the free flow of spinal fluid and drugs. Because of the fact that extensive cord lesions were frequently associated with a large quantity of subtentorial fluid, sudden deaths from impaction were commoner. In one sudden death adhesions produced in the upper part of the cord caused death by strangulation in the same manner as that reported by Flesch and Péró.[7] The autopsy of a child with severe myelitis, who died in another hospital, has been published by Armstrong.[8]

(4) Tuberculous Pericarditis: Tuberculous pericarditis was responsible for only one of the fatal meningeal cases, although it had been present clinically in two other meningeal cases. The increasing frequency of this disease has been pointed out.[9] In one of the meningeal cases cardiac arrest occurred during the craniotomy needed to relieve the intracranial pressure. Thoracotomy was done and the heart massaged. At this time there were

numerous tubercles seen on the pericardium. The child died from his meningitis six weeks later. No tubercles were present, but there were adhesions between the caseous glands and the pericardium. The death attributed to this complication was in a 12-year-old boy, who appeared from the neurological standpoint to be recovering from his meningitis. His general deterioration, especially the weight loss, was progressive. Autopsy showed an extreme degree of adhesive pericarditis.

(5) Medullary Impaction: In three cases sudden death was caused by coning of the medulla. Two of the patients had greatly increased amounts of subtentorial fluid and cord damage. The third case was an abacterial meningitis.

Survivors. — (1) Complete Cures (51 cases): Residual damage is steadily decreasing in degree. The proportion of cures increases steadily as time goes on. Both mentally and physically these children are normal. A number of them have had formal intelligence quotients done and by this measurement present a satisfactory rating of not only normal but superior I. Q.'s. One who had spastic quadriplegia, unconsciousness with continuous twitching, and some convulsions for months leads his class in school. Discontinuance of therapy was considered in his case because of the severity of the disease. Fortunately this was not done. In another, whose I. Q. is 120 five years after her meningitis, it was seven months before consciousness returned. Many of the cured patients had had long illness and the barbaric treatment formerly considered necessary. The discontinuance of intrathecal treatment made possible with isoniazid has made an unbelievable difference in the course of the disease and has permitted better results.

(2) Mental Damage: There are 11 survivors with severe mental damage. Their I. Q.'s range from 20 to 60. In addition, there are two with normal or better I. Q.'s who present such severe organic behavior problems that their survival is of little benefit. Most of these cases were treated in the years 1947-1950. There has been only one mental case since the end of 1951. Two of the recurrences after three years were patients of this type. The picture shown of the brain of one offers sufficient explanation.

(3) Epilepsy: Epilepsy has not been a common sequela of the disease in this series. It is present in two children. In one case the first symptoms occurred three years after his meningitis, which was severe and complicated by myelitis. This child was known to us before his meningitis and was of dull normal intelligence. His mother is also an epileptic. His EEG shows no localized disease. One is therefore in a quandry as to whether the epilepsy is inherited or a result of the infection. The other has a mild spastic hemiplegia. Her I. Q. is low, and she needs sedatives for petit mal attacks.

(4) Spasticity: Six patients are normal except for a mild involvement of a leg. This is being corrected surgically and does not appear to interfere with leading a normal life. Two of the mentally deficient children are still grossly spastic, three years after recovery from the acute illness.

(5) Deafness: Deafness up to the last three years has been the commonest handicap persisting in children otherwise normal. In some of the children with severe brain damage it has persisted too, but is the least of their troubles. Seventy-five per cent of children became deaf during treatment up until intrathecal therapy was discontinued. In most, this cleared up as the patient got better. In some, mild deafness, not sufficient to preclude ordinary school, persisted. In those without brain damage who have remained permanently deaf, previous ear disease had been present in a high percentage of cases. Two had mastoiditis when admitted with tuberculous meningitis. One had a bilateral mastoidectomy two years before. Two had chronic otitis media. The first return of hearing in one case was three and a half years after the acute illness. Four mentally bright children are so deaf that they attend a school for the deaf. No deafness has developed in any child in the past three years since intrathecal treatment was discontinued.

(6) Blindness: The eyes of all cases of meningitis have been carefully followed by the ophthalmologists. Miliary tubercles have only been seen twice in meningeal cases, oftener in nonmeningeal miliary disease. Tuberculomata have been seen twice. Optic edema has indicated the need of relieving cerebral hypertension. By far the commonest finding has been white, thickened, and avascular discs suggestive of primary optic neuritis. This finding was almost constant in the early cases and suggested that blindness would be permanent. Only two patients remained blind after the acute illness. One of these is still blind. This child was a severe case, unconscious seven months and markedly hydrocephalic. She is now normal except for her blindness. She has an I. Q. of 120 and attends the school for the blind. The other patient with blindness that persisted for three and a half years before vision rather suddenly began to come back presented a different picture. Her blindness came on suddenly during the acute stage of the disease. Her fundi were normal, and her case was considered one of interstitial optic neuritis. Her vision is now, five years after her meningitis, good enough to permit school attendance.

(7) Hydrocephalus: Internal hydrocephalus is found in most cases of tuberculous meningitis, whether treated or not. It is not in itself a killer nor necessarily associated with mental change. The blind child mentioned above was the worst case in the whole series. Her head remains larger than normal by measurement, but not to the eye of the public. Most of them recede with recovery to the stage that, although measurement shows an increased head size, it is not apparent in appearance. In some cases the head returns to normal size. Most of the mentally ill show gross internal hydrocephalus, when air encephalograms are done. Three showed external hydrocephalus, which has rarely been seen at autopsy.

(8) Cerebral Calcification: Radiological studies have been made of the skull, in 12 cases, up to five years after the acute disease. Surprisingly little calcification has been shown. Russell and MacArthur [10] reported calcification in 10 of 13 patients who had survived long enough for its development. In two of ours a fair amount of calcification was apparent in and about the pituitary fossa. In one it was excessive. This child presents a Cushing's syndrome. Diffuse calcification resembling the picture of cerebral toxoplasmosis was seen in one, and in a very slight degree in one other. In the most marked case, the previous plate taken two years after the acute attack showed nothing. The second positive x-ray was taken four years after the acute illness. It is impossible to say whether the shadows seen were calcified tubercles or vascular lesions.

COMMENT

The discovery of streptomycin for the first time made it possible to salvage some cases of tuberculous meningitis, which with few exceptions prior to this had always been fatal. It was not long before it was realized that the tubercle bacillus became insensitive to it This led to the first improvement over using this drug alone: A second bactericidal or bacteriostatic drug was added which delayed the development of insensitivity. As time elapsed, more and better drugs were developed until, as far as chemotherapy was concerned, a peak was reached in its possibilities. Still some patients died, and some suffered from severe residual damage. This resulted in reverting to a consideration of the host, and possibly bettering results by treating him.

Some simple measures that had been obvious for years but defeated in achieving success because the organism was not destroyed again came into the picture. These were, first, the recognition of the obvious necessity of reducing intracranial pressure if the patient was to survive long enough for chemotherapy to be effective. Second, it was soon obvious that the basilar collar of granulations or cord block was very little altered by drugs, and some other measure was needed. Tuberculin had been known to help reduce the granulations as far back as 1891 (Virchow [11]). Its use was again revived by the workers at Oxford, England. It proved

efficacious, even if strenuous, treatment. Others used streptokinase-streptodornase (Varidase) or cortisone with seemingly good effect. Third, it became very apparent that disturbance of electrolyte balance in young children could be just as fatal in the meningitides as in other childhood diseases. Determining the nature of the imbalance and giving the treatment indicated added to a further salvaging of lives.

The need for some substance that would stimulate host resistance has been felt by many. No satisfactory substance has been found as yet, although certain workers have found that certain non-ionic detergents were capable of stimulating host resistance in mice.* These are too toxic to use in humans. In our work here on the Middlebrook-Dubos hemagglutination test,[14] it was noted that BCG stimulated a significant rise of antibody titer in animals. Six "vegetable" cases were given BCG at weekly intervals. Five of the six recovered, whether antibody stimulation was contributory or not. To date, there is no established way of stimulating host resistance.

Prophylaxis is an important therapeutic measure in this disease as in others. It goes without saying that isolation of tuberculous cases is a prime consideration. There are two more active means, one a tried and proved one (BCG) and the second, possibilities inherent in the project initiated by Dr. Edith Lincoln of giving patients with uncomplicated primary disease isoniazid to protect against the development of this complication. The former of these has already proved its merit when given a chance, as in the Scandinavian countries. Our own BCG studies would bear this out. Since the second is in process of study, its effectiveness remains to be proved.

The results of treatment became increasingly gratifying. They are certainly best where all known measures against the organism plus helping the host are used.

SUMMARY

This paper reviews the results obtained in 134 cases of tuberculous meningitis plus 17 of abacterial meningitis in tuberculous children.

The biggest advance made since streptomycin was discovered has been the availability of isoniazid. This drug with certain proved invasive merits as well as antibacterial ones, coupled with the possibility of discontinuing intrathecal therapy, has made better results obtainable in a much pleasanter way for the patient.

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Case Reports

HEMOGLOBIN-S-THALASSEMIA DISEASE

Report of a Case in a Negro Child

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HEMOGLOBIN-S-thalassemia disease (microdrepanocytic disease) is the result of double heterozygosity for the genes of hemoglobin S and thalassemia. Its highest incidence would be expected where areas of high density of thalassemia and sicklemia are geographically proximal. Sicily and southern Italy are such places, and recently Silvestroni and Bianco * have reported 57 cases in 28 families from there. In this country only 22 cases have been reported,† most of them in patients of Sicilian, Italian, or Greek ancestry. Indeed, most of the cases of sickle-cell anemia reported in white persons, in retrospect, were probably examples of S-thalassemia, and Chernoff [15] in his excellent review estimates that there are at least 14 of these in the literature. Since thalassemia minor is known to occur also in the Negro,[16] and we have seen six such cases, S-thalassemia would be expected to be found in this race. There are five reports ‡ of 13 instances of this occurrence, 7 in children. It is the purpose of this paper to present another case in a Negro child, emphasizing the characteristic features of the electrophoretic pattern and other hematologic data.

Submitted for publication Nov. 8, 1955.

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* References 1 and 2.

† References 3 through 14.

‡ References 4, 9, 11, 13, and 14.

A 7-year-old Negro boy was admitted to the University Division, Pediatric Service, at Kings County Hospital on Jan. 1, 1955, with the chief complaint of severe lower abdominal pain for one day. On the previous day he had noted the sudden onset of severe pain, beginning in the left thigh and radiating up to the lower abdomen. The pain was spasmodic, lasting for one to two minutes, then disappearing, only to return again after a minute. The pain was severe enough to prevent walking. The only other complaint was that of frequency of urination during the same time period. The child had been a full-term baby with subsequent normal development and activity. The only relevant illness occurred one year previously, at which time he had a similar episode of abdominal pain for which he entered the hospital. No specific diagnosis was made, and the pain subsided spontaneously within three days. He had never had attacks of bone and joint pain or jaundice, nor had he had leg ulcers. No pallor had been noted.

The mother and her relatives knew of no instance of blood dyscrasia in their family. The father could not be reached, either for questioning or for blood studies. Both parents were American Negroes. The only sibling, a 5-year-old boy, had been well since birth.

The patient was a well-nourished and well-developed Negro boy, in severe abdominal distress. The temperature was 100.6 F. He preferred the knee-chest or prone position and protested against any change. There were no skin lesions and no facial abnormalities. The pharynx was mildly injected, and the tonsils were enlarged. The apical rate of the heart was 80 per minute. A systolic murmur of Grade 2 intensity was heard best at the apex and was not transmitted. The abdomen was scaphoid, and there were tenderness and involuntary muscle spasm over the lower abdominal quadrants. No rigidity or rebound tenderness was elicited. No liver, spleen, or other masses were palpable. There was moderate tenderness over both thighs.

On admission the Hgb. was 9.0 gm. per 100 cc., the RBC 4,100,000 per cubic millimeter, the WBC 11,800 per cubic millimeter, with a differential count of 72% neutrophiles, 20% lymphocytes, and 8% monocytes. The urine contained no albumin, sugar, or acetone, but 10 WBC per high-power field were seen in the microscopic examination of an uncentrifuged specimen. There were no casts or RBC.

The abdominal pain persisted in severity, and an acute abdominal emergency was suspected. A roentgenogram of the abdomen and an intravenous pyelogram were noncontributory. The surgical consultant found no indication for operative intervention. The patient required acetylsalicylic acid (aspirin), codeine, and then meperidine (Demerol) for relief of pain. He was also treated with penicillin and tetracycline. Despite the discomfort, the child maintained an adequate nutritional intake and did not vomit or complain of nausea. A sickle preparation showed sickling. During the next few days the temperature remained between 100 and 102 F, but the abdominal pain gradually subsided, and on the fifth day of hospitalization the boy became asymptomatic, although fever persisted for another few days. He was then discharged, to be followed in the outpatient department of the hematology service.

Laboratory investigation during hospitalization showed a sedimentation rate of 5 mm. in one hour (Wintrobe), a negative Mantoux (0.1 gm. old tuberculin), and beta-hemolytic streptococci and

Sickle-Thalassemia—Laboratory Data

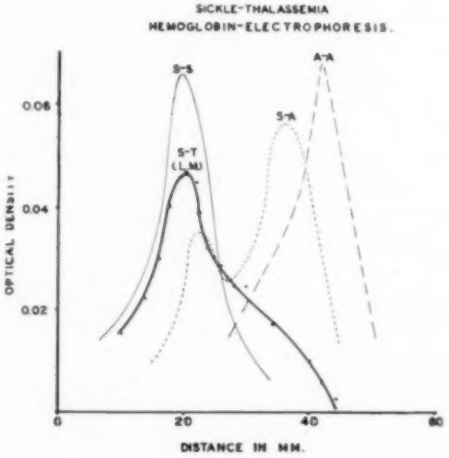
Date (1955)	1/3	1/6	1/24	3/8
RBC (10/cu. mm.)	4.09	4.00	4.44	3.72
Hemoglobin (gm. %)	8.5	8.1	10.1	10.2
Hematocrit (%)	27	26.3	31	32
MCV (cu. μ)	66	66	70	86
MCHbC (%)	32	31	32	32
MCHb ($\mu\gamma$)	21	20	22	27
Reticulocytes (%)	2.0	2.0	....	1.1
Icteric index (units)	5	5	5	5

Staphylococcus aureus in the nose and throat cultures. The antistreptolysin titer was 250 units. The NPN was 34 mg. per 100 cc., and the total bilirubin was less than 1 mg. per 100 cc. X-rays of the skull and long bones were normal, but those of the small bones showed slight thinning of the cortical borders of the osseous structure and minimal demineralization.

A summary of the hematologic data is given in the Table. The blood smears consistently showed microcytosis, hypochromia, marked variation in size and shape of the erythrocytes, and large numbers of target cells. Basophilic stippling and polychromasia were noted in an occasional erythrocyte. Less than 1% of the red blood cells were in the irreversible sickle shape. When exposed to sodium bisulfite in a sickle-cell preparation, the cells assumed the holly-wreath form, from which some progressed to crescentic forms with long filaments. Some of these, as well as some of the wreath forms, were observed to lose their filaments or split irregularly in a process of fragmentation not previously observed.

Filter-paper electrophoresis,[17] performed soon after admission and again three months later, showed about 90% hemoglobin S, most of the remainder migrating slightly more slowly than normal (Chart). An alkaline denaturation test[18] showed about 4% of the hemoglobin to be alkali-resistant (hemoglobin F). This indicated that the remainder of the hemoglobin, 6%, was hemoglobin A.

The Sherman test[19] showed that 35% of the circulating erythrocytes were in the sickled shape. The osmotic fragility was decreased, with hemolysis beginning at 0.38% NaCl and complete at 0.28% NaCl. The plasma iron was 32γ per 100 cc., the unbound iron-binding protein 150γ per 100 cc., and the degree of saturation was 17%. After six weeks of iron therapy these values reached normal levels of 98, 182, and 35, respectively. Hereafter, repeated sickle preparations showed sickling of the long



Hemoglobin S, 90%; hemoglobin A and F, 10%. Since the alkaline denaturation test showed 4% hemoglobin F, there is presumably 6% hemoglobin A.

filamentous type without the peculiar fragmentation in the intermediary phase.

Investigation of the mother's blood showed a hemoglobin of 11.5 gm. per 100 cc., RBC count of 4,860,000 per cubic millimeter, hematocrit value of 37%, mean corpuscular volume (MCV) of 75 cu.μ, mean corpuscular hemoglobin concentration (MCHbC) of 31%, and mean corpuscular hemoglobin (MCHb) of 13.5$\mu\gamma$. The blood smear showed many hypochromic microcytes, oval cells, and target cells. A rare stippled erythrocyte was seen. The sickle-cell preparation was negative. The red blood cells showed increased resistance to hypotonic saline solutions. Electrophoresis showed that all of the hemoglobin was the normal A-type. The alkaline denaturation test showed no hemoglobin F. The

plasma iron was 96γ per 100 cc., the unbound iron-binding protection was 135γ per 100 cc., and the saturation was 42%. Because of these findings the mother was considered to have thalassemia minor.

COMMENT

The diagnosis of S-thalassemia in our patient was arrived at by the following consideration:

The presence of recurrent severe abdominal pain in a Negro child who had an anemia and 100% sickling first suggested the diagnosis of sickle-cell anemia. However, the scarcity of irreversible sickle cells in the stained blood smear would have been most unusual in S-S disease and indicated a sickle-cell variant such as S-C or S-thalassemia.

The low MCV associated with a low plasma iron value suggested concomitant iron-deficiency anemia. However, since a course of iron therapy for six weeks did not raise the hemoglobin above 10 gm. per 100 cc., and since the low MCV persisted despite the restoration of normal iron values, the diagnosis of S-thalassemia seemed likely. (The other sickle variants, just as S-S disease, have normocytic, normochromic erythrocytes). The blood smear continued to show the microcytic hypochromic poikilocytes typical of thalassemia.

Furthermore, the electrophoresis of the hemoglobin together with the alkaline denaturation test showed 90% hemoglobin-S, 6% hemoglobin A, and 4% hemoglobin F, a pattern considered [14] characteristic of S-thalassemia.

The Negro mother was thought to have thalassemia minor because of the presence of a microcytic hypochromic anemia with normal plasma iron values, along with increased osmotic resistance of the erythrocytes. The presence of 100% hemoglobin A by electrophoresis excluded the possibility of an abnormal hemoglobin trait such as C, D, or S, and thus meant that the mother could have endowed her offspring with the gene for hemoglobin A only. Presumably the father (who was unavailable for study) possessed the S-trait.

The high percentage of hemoglobin S (90%) in a disease that is heterozygous for hemoglobin S deserves comment. In six § of the seven reports on the electrophoretic pattern in this condition 60% to 88% of the hemoglobin was S. An exceptional amount, 100% hemoglobin S, was reported by Humble and his associates.[10] Since the pattern is indistinguishable from that of sickle-cell anemia (S-S disease), the validity of the dignosis has been questioned,[15] although the mother had thalassemia (and no sickling) and the father had sickle-cell trait. Most of the patients with heterozygous combinations of thalassemia with abnormal hemoglobins such as C,[20] E,[21] and G [22] have shown a preponderance of the abnormal hemoglobin of about 70% also. This has been interpreted [23] to mean that the thalassemia gene depresses the formation of normal hemoglobin A, so that a greater amount of abnormal hemoglobin is formed. An alternate explanation is that the presence of the thalassemia gene permits greater expressivity of the gene for the abnormal hemoglobin. In other heterozygous hemoglobin diseases, such as S-C disease, there are approximately equal amounts of the two hemoglobins, as would be expected.

Since in no instance of S-A (sickle trait) does hemoglobin S exceed 45%, the electrophoretic pattern of the sickle trait cannot be confused with that of S-thalassemia, in which the hemoglobin S exceeds 60%. Furthermore, hemoglobin F is not increased in sickle-cell trait. However, there is a potential source of confusion between the pattern of S-thalassemia and that of S-S disease. Our patient had a very typical pattern of S-thalassemia with 90% hemoglobin S, 6% hemoglobin A, and 4% hemoglobin F. The S+A+F pattern is considered by Singer and his associates [14] to be particularly characteristic of S-thalassemia, since there is no hemoglobin A in a patient with S-S disease who has not been transfused, and who may have S and F only. Other less typical pat-

§ References 4, 5, 7, 9, 11, and 14.

terns can occur in S-thalassemia, since three ‖ of nine cases reported ¶ did not have increased amounts of hemoglobin F, and thus had only hemoglobin S and hemoglobin A. Cases having only hemoglobin S and hemoglobin F can also be expected.

In addition to the electrophoretic pattern, there are morphological characteristics of the erythrocytes which are important diagnostically in differentiating sickle-thalassemia from sickle-cell anemia. The blood smear simulates that of thalassemia rather than that of sicklemia because of the presence of marked microcytosis, hypochromia, and poikilocytosis. (In S-S disease the red blood cells are normochromic, normocytic.) Since concomitant iron-deficiency anemia can also produce microcytosis and hypochromia, the presence of a normal plasma iron value can exclude this possibility and support the diagnosis of S-thalassemia.

In regard to the genetics, the absence of sickling in one of the parents immediately excludes the possibility of sickle-cell anemia (S-S) and suggests the presence of a sickle variant. If the nonsickling parent has thalassemia minor and the other parent has sicklemia, the diagnosis of sickle-thalassemia is corroborated. However, kinship studies by Powell and co-workers [3] and Silvestroni and Bianco # have included the occurrence of a case of S-thalassemia as the result of the mating of a normal person and one with S-thalassemia. It has therefore been concluded that the gene for thalassemia is located at a different site on the chromosome (or on a different chromosome), from the hemoglobin S and is not a paired allele as are all the other hemoglobins with the exception of F.

The clinical manifestations * of the disease vary from none to severe crises, such as occur in S-S disease. However, on the whole, S-thalassemia is less severe than S-S and is often not diagnosed until adult life, although symptoms usually date back to childhood. Mild bone and joint pains are common. Abdominal pain of the severity seen in our patient is unusual. The hemoglobin is usually above 8 gm. per 100 cc., and hemolytic crises are infrequent and mild. The most constant feature has been splenomegaly, which has been present in over three-fourths of the cases. (Our patient did not have a palpable spleen.) Although bone x-ray changes have usually been minimal, a few cases of aseptic necrosis of the head of the femur have been reported.[12] Leg ulcers are very rare.

‖ References 4, 11, and 14.

¶ References 4, 5, 7, 11, and 14.

References 1 and 2.

* References 15 and 23.

SUMMARY

S-thalassemia disease was found in a 7-year-old Negro boy. The only clinical manifestations were two attacks of abdominal pain and a mild anemia. The hematologic findings of special diagnostic significance were the following:

(1) An electrophoretic pattern showing 90% hemoglobin S, 6% hemoglobin A, and 4% hemoglobin F.

(2) The virtual absence of irreversible sickle cells in the blood smear, although the sickle-cell preparation showed 100% sickling.

(3) Marked microcytosis, hypochromia, and poikilocytosis of the red blood cells, with many targets, associated with normal plasma iron.

(4) The presence of thalassemia minor in the Negro mother.

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INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM IN INFECTIOUS MONONUCLEOSIS IN CHILDHOOD

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INFECTIOUS mononucleosis with manifestations involving the central nervous system is apparently uncommon in childhood. Although over 100 cases with neurologic signs have been reported in all age groups, only 11 of these were in children. Specifically, convulsions have occurred in a total of 13 cases, but in only 4 were the patients less than 16 years old. The purpose of this paper is to report a child with infectious mononucleosis whose presenting sign was a grand mal seizure and to review some of the findings gathered from the literature.

REPORT OF CASE

A 9-year-old white boy was admitted to the pediatric service of the Grace-New Haven Community Hospital on Nov. 8, 1954, for evaluation of a grand mal seizure. The youngest of 10 normal children, he had always been in good health, somehow escaping the usual contagious childhood diseases. Two weeks prior to admission, he had had a mild upper respiratory infection, was treated with acetylsalicylic acid and cough medicine, and recovered without incident. The day before admission he complained to his mother of headache and lethargy. His temperature was normal, and he was put to bed, where he slept well through the night. When he arose the next morning he was noted by his mother to have a staggering gait. He again complained of a headache, ate some cereal, and returned to bed. About two hours later his mother, hearing strange noises, entered his room and found the patient having a convulsion. He was immediately taken to his local hospital. Upon arrival there, he had stopped convulsing but was semistuporous and restless. He was given 1 grain (0.06 gm.) of amobarbital (Amytal) sodium. A lumbar puncture was done, and the cerebrospinal fluid contained 17 cells (80% polymorphonuclear cells and 20% mononuclear cells) and a spinal fluid protein of 45 mg. per 100 cc. Consequently, as this occurred during the height of the poliomyelitis season, he was transferred to this hospital, where, soon after arrival, he had another generalized seizure.

Past and family history were entirely negative.

Physical Examination.—On admission his temperature was 37.3 C; pulse rate 96; respiration rate, 30, and blood pressure, 110/60. He was a husky restless semistuporous white boy who was thrashing about in bed and responded only to painful stimuli. The state of hydration was good, and there was no rash. Funduscopic examination was normal. The tonsils were moderately enlarged and slightly hyperemic but without exudate. Lymphadenopathy was confined to small bilateral tonsillar nodes. There were no meningeal signs. The heart, lungs, and abdomen were normal. Neurological examination showed absence of abdominal and cremasteric reflexes in addition to the state of stupor already mentioned.

Laboratory Examination.—Another lumbar puncture was performed. The fluid was under normal pressure and contained 30 WBC (16% polymorphonuclear cells and 84% mononuclear cells). The protein was 51 mg/100 cc.; sugar, 134 mg/100 cc., and chlorides, 134 mEq/L. Spinal fluid culture was negative. Peripheral blood: hemoglobin, 14 gm/100 cc.; WBC, 11,700. Urine was normal. The reaction to the tuberculin test was negative. Skull films were normal. NPN was 16 mg/100 cc.; fasting blood sugar, 105 mg/100 cc., and electrolytes were all normal. Nose and throat culture grew out beta-hemolytic streptococci.

Course.—During the afternoon of admission the patient gradually became more rational and less restless, and by evening he was taking fluids well. The morning after admission he was a fully oriented happy boy. The tonsils were injected, cryptic, and covered with a patchy exudate. A barking cough was present. There was splenic fullness to percussion, though no definite spleen tip could be palpated. Neurological examination was negative except for questionable diplopia on extreme lateral gaze.

Received for publication Oct. 31, 1955.

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The white blood cell count was 8,200, with 43% polymorphonuclear cells, 22% lymphocytes, 6% monocytes, and 29% atypical lymphocytes—so-called Downey cells. Heterophile antibody level was 1:640 before absorption and 1:320 after absorption with guinea pig kidney. Direct and indirect Coombs tests were negative. Results of liver-function tests done on the fifth hospital day were as follows: bilirubin, direct-reacting, 0.04 mg/100 cc.; total, 0.08 mg/100 cc.; cephalin flocculation, 2+; thymol turbidity, 4.9 units; thymol flocculation, 1+. Alkaline phosphatase was 11.0 units. No bile was present in the urine. Viral studies of the blood, cerebrospinal fluid, stool, and throat disclosed no poliomyelitis virus. The blood continued to contain approximately 20% atypical lymphocytes until the time of discharge. Further x-ray studies showed normal heart size, enlarged superior mediastinal nodes, and definite enlargement of the liver and spleen. An electroencephalogram taken on the fourth hospital day was read as showing diffuse but nonspecific changes of only moderate degree and without localizing signs.

The day after admission the patient was started on an eight-day course of penicillin intramuscularly for treatment of his beta-hemolytic Streptococcus infection. In spite of this he continued to have daily temperature elevations above 38.5 C for the first six days in the hospital. On the eighth hospital day his heterophile antibody level was 1:640 before absorption and 1:160 after absorption with guinea pig kidney. His course was otherwise uneventful, and he was discharged on the ninth hospital day. Follow-up studies in the outpatient clinic showed no apparent neurological residua.

COMMENT

The present concept of infectious mononucleosis is that it is a generalized systemic disease of unknown origin with cellular infiltration in almost every organ of the body—the clinical picture varying with the predominant site of involvement. When the nervous system is involved, the manifestations also vary, depending on the site that is implicated.

Reports of histopathologic examination in fatal central nervous system cases show findings that resemble those seen in other virus infections, with perivascular mononuclear cuffing, occasional small hemorrhages, and mild degenerative changes in the brain substance. Distortion of the Purkinje cells, edema, and congestion and mononuclear infiltration of the meninges may also be found. These changes not only occur in the cerebrum and meninges but may also be seen in the cerebellum and the spinal cord, where they primarily involve the anterior nerve roots at any and all levels. Even when no neurologic signs or symptoms had been recognized, postmortem examination done on a convalescent case of infectious mononucleosis who died after an automobile accident showed varying degrees of central nervous system involvement.[9]

In addition to what are considered to be the usual signs and symptoms of infectious mononucleosis, those cases showing nervous system involvement may be classified into six groups:

1. Serous meningitis, with fever, headache, clear sensorium, photophobia and other eye signs, and nuchal rigidity. The cerebrospinal fluid findings are entirely normal except for elevation of the pressure.

2. Meningitis, with fever, headache, nuchal rigidity, and abnormal reflexes. The cerebrospinal fluid usually shows an increase in cells, protein, and pressure.

3. Encephalitis, presenting with or without fever, but with fever usually developing later, headache, vestibular signs, lethargy, irrationality, and other disturbances of the sensorium. The cerebrospinal fluid protein and pressure are usually elevated, but with little or no increase in cells.

4. Acute polyneuronitis (Guillain-Barré syndrome), showing widespread, usually symmetrical, flaccid paralysis involving the cranial or peripheral nerves (or both), loss of reflexes, sensory losses, absence of fever in many cases, and elevation of the spinal fluid protein without an increase in cells—that is, albuminocytologic dissociation.

5. Peripheral neuritis, with flaccid paralysis limited to an isolated group of muscles, with or without fever. The cerebrospinal fluid usually is normal.

6. Optic neuritis, with varying disturbances of vision, papilloretinal edema, and hemorrhages and no changes in the spinal fluid.

Findings in Pediatric Patients with Neurologic Complications of Infectious Mononucleosis

Age, Yr.	Sex	Signs and Symptoms	CNS Manifestations	Spinal Fluid Findings	Blood Findings	Heterophile Agglutination	Outcome	Neurological Diagnosis	Author
14	F	Headaches and coryza with slight elevation of temperature at onset	Blurring and dimness of vision developed 2 wk. after onset; eyegrounds showed edema and hemorrhage involving discs	Cells, 6 leucocytes; protein, 55 mg.	WBC, 8,000; P, 20%; L, 73%; M, 7%; B, 2%; "many atypical lymphs"	+ at 1:866	Complete recovery	Optic neuritis	Bonynge [4]
10	F	Swelling of cervical glands and malaise at onset; "acute tonsillitis" 1 wk. later, followed by vomiting and weakness	Two weeks after onset developed lethargy and + Kernig signs; later developed muscular weakness, hyperesthesia, and hyperalgesia with variable neurological findings	Cells, 9 leucocytes; protein, 400 mg.; later returned to normal	WBC, <5,500, with lymphocytosis on repeated examinations; atypical lymphocytes not mentioned	+ at 1:256	Complete recovery	Encephalomyelitis	Gellebter [5]
3	M	Fever, lethargy, and anorexia at onset; developed staggering gait next day; became semistuporous 4 days later	Six days after onset developed staggering gait with hypotonia; vertical nystagmus; slight papilledema; showed moderate nuchal rigidity with positive Brudzinski sign	Cells, 195 (40% monocytes); protein, 45 mg.; sugar, 89 mg.	WBC, 9,200; P, 50 (47/3); L, 30; AL, 20	+ at 1:128	Complete recovery	Meningoencephalitis	Karpinski [3]
9	M	Headache and fever at onset; symptoms persisted and projectile vomiting appeared 3 days later	Four days after onset showed slight nuchal rigidity and questionable Brudzinski and Kernig signs	Cells, 35 (90% monocytes); protein, 76 mg.; sugar, 82 mg.	WBC, 6,000; P, 42 (41/1); L, 29; M, 2; B, 3; AL, 24	+ at 1:128	Complete recovery after 3d hospital day	Meningoencephalitis	Karpinski [3]
9	M	Became lethargic and started progressive paralysis at onset; 2 days later developed headache, sore throat, and cervical adenopathy; 5 days later developed staggering gait, "acted intoxicated"	Eight days after onset, on admission, showed nuchal rigidity, semistupor, hypotonia, positive Kernig sign; lower extremities were flaccid	Cells, 36 (100% monocytes); protein, 30 mg.; sugar, 83 mg.	WBC, 10,500; P, 55 (48/7); L, 11; E, 1; AL, 33	+ at 1:1024	Paralysis of lower extremities and urinary incontinence after 5 mo.	Encephalomyelitis	Karpinski [3]
2	M	Developed fever, anorexia, irritability, and lethargy at onset; had shotty nodes and hepatomegaly and splenomegaly 3 days later	Three days after onset admitted with symptoms noted; no neurological findings, no nuchal rigidity	Cells, 297 (100% monocytes); protein, 10 mg.; sugar, 79 mg.	WBC, 11,500; P, 23 (20/3); L, 32; E, 3; AL, 42	+ at 1:32	Complete recovery	Encephalitis	Karpinski [3]
6	M	Bilateral otitis media (suppurative), inguinal pain, pain in legs at onset; 1 wk. later developed weakness in legs	Three weeks after onset admitted with symmetrical weakness of both lower legs, right facial paresis, absent AJ and KJ *	Cells, 2; protein, "slight increase"; 2 wk. later essentially the same	WBC, successive counts ranged from 13,120 to 7,960; atypical lymphocytes, from 8% to 77%	Not reported	Slight residual weakness	Guillain-Barré syndrome	Klovstad [6]
6	M	Symptoms of URI at onset; later developed generalized lymphadenopathy and splenomegaly	Four weeks after onset developed blurred vision; CNS examination otherwise negative and fundi were normal	Not reported	WBC, 10,650; P, 33 (20/13); L, 52; M, 7; AL, 8	+ at 1:224	Complete recovery	Retrobulbar neuritis	Shechter [7]
8	M	Sore throat and cervical adenopathy at onset; 12 days later developed headache, fever, and splenomegaly	Two weeks after onset became irritable, then irrational; began to have frequent convulsions; later became unresponsive to strong stimuli; developed coma, opisthotonus, extensor spasm, and hyperpyrexia	Cells, 7, 21, 2; protein, 256, 148, 178 mg. on successive examinations	WBC, 25,000, later decreased to 10,000; atypical lymphocytes were seen on 5th and 14th hospital days	+ at 1:1024	Complete recovery	Encephalitis	Walsh [2]

* AJ, ankle jerk; KJ, knee jerk.

In their review of the literature in 1950, Bernstein and Wolff [1] found 35 cases of central nervous system involvement in infectious mononucleosis that they believed have an entirely acceptable diagnosis. Of these, five patients had associated convulsions, the youngest being 15 years of age.[10] Since that time Walsh and co-workers [2] reviewed the pediatric literature and found seven substantiated cases involving the nervous system. All investigators emphasize that the recognition of such involvement is rare but point out that this complication probably occurs relatively frequently. In no other previous report was a convulsive seizure listed as the presenting symptom.

Although infectious mononucleosis is distributed equally between the two sexes, it is of some interest to note that central nervous system symptoms appear more commonly in males. Of a total of 13 cases with convulsions, 9 have been males.

There is extreme variation in the time of appearance of neurological signs or symptoms. In several instances these have preceded the usual signs of infectious mononucleosis by as much as a week. In others they came on simultaneously and then may have subsided separately or at the same time, while in still others the neurological signs appeared several weeks after the usual signs of the disease had disappeared. Thus, it would appear that nervous system involvement is not an antibody response but is, rather, the result of actual invasion of the nervous system by the agent causing the disease.

Changes in the spinal fluid have been reported in patients with infectious mononucleosis who did not have any central nervous system manifestations whatever,* while in others the converse was true—patients with abnormalities may have had a normal cerebrospinal fluid. When they occurred, alterations in the spinal fluid of reported cases have been limited to increases in the cellular composition, protein element, or fluid pressure. The pleocytosis consists mainly in an increase of mononuclear cells. Reports on the levels of sugar and chlorides have indicated that they have been consistently normal. Although infectious mononucleosis may produce false serologic reactions for syphilis, there have been no reports of positive reactions of the spinal fluid.

Only one of several investigators who have investigated the spinal fluid for heterophile agglutinins has noted its presence.† Our patient, unfortunately, was not tested in this respect. In certain cases there may be an absence of pleocytosis, even though the spinal fluid protein is markedly elevated. That this may be a late finding in the disease is illustrated by one of Karpinski's [3] patients, in whom the spinal fluid early in the course of the disease contained 36 cells per cubic millimeter, with a protein of 30 mg/100 cc., while on the 20th hospital day there were no cells and a protein of 300 mg/100 cc.

The prognosis for such patients is usually good. Complete recovery from the neurological manifestations usually takes place rapidly, but permanent residual damage and even deaths have been reported, usually secondary to involvement of the brain stem or respiratory center.

Treatment is confined to supportive measures, since no specific therapy as yet is available.

SUMMARY

A case is reported of infectious mononucleosis in a 9-year-old boy whose presenting sign was a grand mal seizure.

The pediatric literature on the subject is reviewed and discussed.

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EPIGNATHUS

Survey

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THE TERM "epignathus" as commonly used refers to any parasitic growth coming out of the mouth of the host, though the literal translation means a parasite arising from the mandible. The origin of the parasites in the series and case reports noted was definitely from the upper jaw rather than from the mandible.

The following report is of the first and only epignathus recorded at the Milwaukee Children's Hospital since 1924. The rarity of this particular abnormality interested us so that a search of the literature was made as a survey along with the following specific case report. The English language literature was surveyed back to 1936 and, as the bibliography indicates, is rather scanty because of the rarity of the condition.

REPORT OF CASE

This was the fourth pregnancy of a white Rh-negative mother who had previously had one spontaneous abortion and had borne three children, including one set of twins. Prepartally there was an episode of vaginal bleeding at three months' gestation, not repeated during the course of the pregnancy. Labor began spontaneously at slightly over eight months' gestation, and polyhydramnios noted on admission to the hospital was so marked that no fetal motions nor fetal heart tones could be objectively recorded, though the mother said she did feel the fetus move. Immediately following artificial rupture of the membranes there was spontaneous delivery of a white boy, estimated birth weight of about 4 lb.

Extending from the mouth of the infant was a roughly spherical mass about the size of a small grapefruit, with a well-formed finger on the upper surface. This mass was partially solid, with a cystic portion which was tense, and so aspiration was attempted to reduce its size. About 80 cc. of clear yellow fluid was obtained, and after this aspiration the tumor measured 6×6×3 cm. The attachment to the palate was very broad-based. Respiratory difficulty was present at birth and was alleviated only by introduction of a small airway, which depressed the lower jaw and raised the mass.

The child was taken from the hospital of birth to the Milwaukee Children's Hospital via police ambulance, under oxygen, for definitive therapy. An immediate tracheotomy, after the introduction of an endotracheal tube, was done in order to establish a permanent airway. Excision of the mass was impossible at this time both because of the poor condition of the child and the size of the tumor, with its broad base attached in the palate area. The child's condition deteriorated rapidly in spite of all supportive measures, and he died about 10 hours after birth.

At the time of postmortem examination an attempt was made at a surgical excision of the mass to see whether or not such removal would

Photograph taken immediately after birth.

Submitted for publication Jan. 9, 1956.

have been possible during life. The mass weighed 55 gm. after separation and was covered with skin and lanugo. Its shape was somewhat irregular, and it measured 6×6×3 cm. One finger-like projection 3 cm. long with a fairly well-formed fingernail extended from the upper surface. The broad base was attached to the roof of the mouth and the edges of the cleft palate and covered an irregular area 3 cm. in diameter. Near the attachment the covering of the mass appeared to be of mucosal character. It was believed after this dissection that an attempt at surgical removal would almost certainly have resulted in death on the table from hemorrhage.

The tongue was found to be normal. The remainder of the postmortem examination revealed only pulmonary atelectasis, with a hyaline membrane. The skull was opened, and it was found that there was no connection between the mass and the base of the skull.

Gross and microscopic examination of the epignathus itself showed a variety of structures, including connective tissue, skin with appendages, a finger with bone and fairly well-formed joints, and cysts lined by columnar epithelium, with smooth muscle in the walls. One cyst was lined by squamous epithelium and contained desquamated epithelial cells.

COMMENT

Epignathus, fortunately because of the poor survival rate, is a very rare anomaly and varies greatly in structure. These variations include simple "compound polyps of the pharynx" or hairy polyps, larger masses containing tissues representative of all three germ layers, tumors with recognizable organs or extremities, and asymmetrical twins.

The site of origin of these masses does not vary quite so much, nearly all arising at or near the midline of the upper jaw. For this reason Ehrich[6] prefers the terms episphenoid, epipalatus, or epuranus to indicate more clearly the fact that the upper jaw is usually involved. Encrania have much the same origin, from the palate or base of the skull, but grow upward as well as, or instead of, into the mouth; these may arise from the pituitary area (Rathke's pouch) or from the sphenoid bone and can extend into the pharynx and even into the mouth.

There is also variation in the theories as to how this malformation develops. Some authors* (the "monozygotic school") believe that epignathi are like dermoids and teratomas in that they all develop from tissue rests within the host. Others† are of the opinion that the anomaly compares with other parasite-host forms of incomplete twinning and is of dizygotic origin because of parallel position, alignment, and development. These latter particularly dislike the term epignathus and prefer the term sphenopagus (or palatopagus) parasiticus. They regard the parasite as being usually an acephalus acardia.

In our case there were several points of special interest. Prepartally the episode of vaginal bleeding and polyhydramnios certainly indicated some abnormality of the fetus. Luckily neither the fetus nor the teratoma was large enough to interfere with the normal processes of labor and vaginal delivery. Also, the fact that twins had previously been born to these parents tends to strengthen the feeling that this teratoma was a poorly developed twin to the host, rather than a tissue or germ-cell rest. The autosite in our case was male; although no special significance is attributed to this fact, it is of some interest, since the autosite in every one of 22 cases in Ehrich's series was a female.

SUMMARY

This is a case report and survey of the recent literature about the rare malformation of epignathus, perhaps better called epipalati or episphenoid (depending on the site of origin), and, to be very technical, also named sphenopagus (or palatopagus) parasiticus.

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Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

NUTRITIONAL AVAILABILITY OF IODINE FROM SEVERAL INSOLUBLE IODINE COMPOUNDS. SIDNEY MITTLER and G. H. BENHAM, J. Nutrition **53**:53 (May 10) 1954.

The authors found that iodine is readily available from the insoluble iodine compounds, 3-5-diiodosalicylic acid, cuprous iodide and thymol iodide. Because of the individual fluctuations in thyroid size and in body weight, it is difficult to compare one iodine compound with another. However, cuprous iodide appears to provide iodine to the thyroid gland as readily as KI, and in one series of experiments, in which an amount of iodine less than optimum was supplied, the cuprous iodide appeared to afford somewhat better protection than did the potassium iodide. Acute and chronic toxicity tests indicated that cuprous iodide and 3-5-diiodosalicylic acid were nontoxic in the amounts required to protect the thyroid gland.

FREDEEN, Kansas City, Mo.

BASAL METABOLISM OF NINETEEN CHILDREN FROM TWO TO TEN YEARS OLD. MINA WOLF LAMB and JONNIE MCCRERY MICHIE, J. Nutrition **53**:93 (May 10) 1954.

The authors present data from 86 basal metabolism determinations on 19 subjects, 2 to 10 years of age. Their results indicate that age alone is an adequate criterion by which to classify the basal metabolism of children. Basal metabolism changes more uniformly with change in size than in age. The results are more constant when expressed per unit of height than per unit of weight or surface area. Their results do not conform with the prediction standards developed by Benedict and Dreyer, but agree closely with those of Talbot and Lewis.

FREDEEN, Kansas City, Mo.

OBSERVATIONS ON TOTAL BODY CHLORIDE IN CHILDREN. DONALD B. CHEEK, Pediatrics **14**:5 (July) 1954.

The distribution of bromide has been used to measure total body chloride in 50 infants and children. Total chloride has been found to follow the differential growth equation. An index of extracellular water has been obtained and followed with the progress of age. It has been found that infants in early life have 40% more chloride per unit weight than adults have. Total chloride per kilogram shows a rapid proportionate decrease during the first year of life.

FROM THE AUTHOR'S SUMMARY.

THE ABSORPTION OF SHORT-CHAIN FATS BY PREMATURE INFANTS. SELMA E. SNYDERMAN, SOLEDAD MORALES, and L. EMMETT HOLT JR., Arch. Dis. Childhood **30**:83 (April) 1955.

Premature infants will absorb short-chain fats without difficulty, presumably because the portal absorption mechanism is unimpaired. The superior absorption of these fats is counterbalanced by their inferior caloric yield.

KELLY, Milwaukee.

THE LYSOZYMIC POTENCY OF THE SERUM OF BLOOD FROM THE UMBILICAL CORD. A. CUTRANEO and F. MUSCOLINO, Lattante **26**:382 (June) 1955.

The lysozymic potency of the sera of blood withdrawn from the umbilical cords of 30 newborn infants was found to be very high. In 12 sera there were found 512 U. F. (Fleming Units), in 13 there were 256 U. F., in 4 there were 128 U. F., and in 1 there were 64 U. F. There was no relation between the weight or sex of the infant and the degree of lysozymic potency. Reports from the literature indicate that healthy children up to one year of age have 64 to 128 U. F. in the sera; as the child grows older, the titer falls.

HIGGINS, Boston.

DETERMINATIONS OF CARBONIC ANHYDRASE IN HEALTHY, PREMATURE, AND DYSTROPHIC INFANTS. B. DE MARCO and F. CUSMANO, Lattante **26**:388 (June) 1955.

Carbonic anhydrase is an enzyme present in the red cells which enables the blood to pick up CO_2 from the tissues and deliver it into the pulmonary alveoli. Using Philpot's method,

determinations were made of the carbonic anhydrase in the bloods of 6 adult men, 10 adult women, 10 healthy infants, 8 premature infants, and 10 dystrophic infants. The results indicate that healthy infants have a titer of the anhydrase about equivalent to that of adults, but that in premature and dystrophic infants the titer is low. This test is recommended as giving an index of the degree of functional maturity and eutrophy of each individual infant.

HIGGINS, Boston.

THE ACTION OF HIGH FREQUENCY SOUND ON REDUCTASES AND PEROXIDASES IN COW'S MILK. A. FERLAZZO, G. LOMBARDO, and G. CUZZOCREA, Lattante **26**:504 (Aug.) 1955.

The enzymatic properties of cow's milk were found to be reduced by exposure to ultrasonic waves in direct proportion to their intensity and duration. The enzymatic inhibition is accompanied by and probably related to the bactericidal effects. These findings are applicable to the preservation and safety of milk.

HIGGINS, Boston.

Prematurity and Congenital Deformities

HYPOPLASIA OF THE MANDIBLE WITH A FALLING BACK OF THE TONGUE AND "CARNAGE" IN INFANTS (ROBIN'S SYNDROME). P. NICOLAJ, Clin. pediat. **37**:378 (May) 1955.

Robin's syndrome is the characteristic picture seen in infants who have hypoplasia of the mandible, pushing back of the tongue (glossoptosis), difficult respiration, retraction of the sternum on inspiration, spells of cyanosis, and poor nutrition. Six cases of this syndrome are reported in infants 17 days to 4 months of age; four of the patients died. The opinion is expressed that the symptoms are not wholly due to the mechanical factors, but that muscle hypotonia due to nervous dysfunction plays a large part.

HIGGINS, Boston.

A RARE MALFORMATION OF THE SACRUM. C. ZUNIN, Lattante **26**:340 (May) 1955.

In the case of a baby with spina bifida and meningocele in the sacral region and with developing hydrocephalus, the sacral vertebrae were found on x-ray to be divided into two equal parts. The single middle anlage of the body of each vertebra must have been split in some manner; according to the usually accepted embryological conceptions, this has not been regarded as possible.

HIGGINS, Boston.

THE MULTIPLE EXOSTOSIS TYPE OF CHONDRODYSTROPHY, ASSOCIATED WITH OSTEOPECILIA IN THE MOTHER. S. NORDIO, Minerva pediat. **7**:811 (July 14) 1955.

This 8-year-old boy had multiple exostoses, involving the cranial bones among others. He was of normal size but of a neurotic and unsocial disposition and subject to epileptic attacks. He also had lenticular fibromata of the skin. A familial characteristic is apparent in that the mother had osteopecilia and fibromata of the skin.

HIGGINS, Boston.

Newborn

THE EFFECTS OF HYPOXIA ON THE RESPIRATION OF NEWBORN INFANTS. HERBERT C. MILLER and FRANKLIN C. BEHRLE, Pediatrics **14**:93 (Aug.) 1954.

The effects of administering atmospheres containing 10% and 12% oxygen to healthy newborn infants of different ages have been studied. Infants under 24 hours of age tended to hypoventilate throughout the period of hypoxia. Infants 6 to 11 days of age hyperventilated for the first two or three minutes and then showed a decrease, although not so marked as observed in the infants under 24 hours of age. Infants 16 to 48 days of age showed the most marked increase in ventilation, but even in these infants it was poorly maintained as compared to responses seen in adults.

Hypoxia produced a slowing of the respiratory rate in all infants except the very oldest. Tidal air was increased at first and then decreased. The increases in tidal air accounted for most of the increase in minute volume seen in the older infants.

Hypoxia increased the incidence of periodic breathing in the two older groups of infants, but had very little effect on infants under 24 hours of age.

Respiratory patterns did not appear to be altered by the hypoxic conditions employed in this study.

It has been postulated that the comparatively weak response to hypoxia made by infants immediately after birth possibly is dependent on relatively poor chemoreceptor reflexes and that the latter increase in strength during the first weeks of postnatal life.

It has also been suggested that the relative inability to induce periodic breathing in infants under 24 hours of age as compared to those several weeks old is further evidence indicating that metabolism of the medullary respiratory centers is to a larger extent anerobic than at the later periods of postnatal life.

FROM THE AUTHORS' SUMMARY.

STENOSIS AND CONGENITAL ATRESIA OF THE SMALL INTESTINE IN THE NEWBORN INFANT. C. IMPERATO and L. LANDUCCI, Lattante **26**:425 (July) 1955.

Five cases of stenosis or atresia of the small intestine in newborn infants are reported. In two cases there was atresia of the jejunum, in one stenosis of the duodenum, in one stenosis of the ileum, and in one a volvulus. Four of the five cases were in premature infants, all five infants died. Since relief of the conditions must usually be surgical, early diagnosis is imperative; x-ray and blood chemical studies proved of diagnostic help. Because of the fact that the condition is usually in premature infants and preoperative preparation is not prolonged, the prognosis in these cases is not very good. In many of the cases the atresia is so extensive that correction is not possible. The malformations may be due to adhesions, to mechanical obstruction, or to abnormal nervous supply to the intestine.

HIGGINS, Boston.

THE STATUS OF CHILDREN BORN OF MOTHERS AFFECTED BY TOXEMIA OF PREGNANCY. D. GABURRO, G. BONIVER, and G. BIANCHI, Lattante **26**:526 (Aug.) 1955.

This is a study of 200 children born of mothers with the toxemia of pregnancy. Forty-five (22.5%) of the infants were born prematurely. Fifteen per cent of the infants died in the neonatal period, thirty-one per cent of the premature infants and ten per cent of the infants born at term. Most of the deaths were due to anoxia.

Anatomical and functional alterations were found in the placenta in almost direct proportion to the duration and severity of the toxemia.

When obstetrical intervention was resorted to, the infant mortality was the lowest in cases of Caesarean section.

Fetal malnutrition was dependent on the duration of the toxemia and on the presence of hypertension in the mother. Nervous lesions in the child were most frequent when there was hypertension in the mother.

HIGGINS, Boston.

THE CEREBROSPINAL FLUID IN THE NORMAL NEWBORN INFANT. H. J. G. WYERS and J. C. W. BAKKER, Maandschr. kindergeneesk. **22**:253 (Aug.) 1954.

Description is given of a series of investigations of the C. S. F. of young infants born at term. The fluid was tapped between 2 and 24 hours after birth. The great majority of the children showed, in protein content, number and type of cells, and collodial reactions, pictures which, in adult subjects, would be regarded as pathological. Owing to the wide differences in the results, it was not possible to determine what should be "normal" values for the C. S. F. in the newborn infant born at term.

Three children delivered by primary Caesarean section showed similar pictures, from which it is concluded that not the birth trauma itself, but other factors were the cause of the abnormal C. S. F. picture.

FROM THE AUTHORS' SUMMARY.

Acute Contagious Diseases

DRINKING WATER: SOURCE OF POLIOMYELITIS INFECTION? HUGH MACDONALD, Illinois M. J. **105**:257-260 (May) 1954.

During epidemics, poliomyelitis virus is found in the stools of persons comprising as much as six per cent of the city population, most of whom show no other sign of the disease. Five times as much chlorine is required to kill poliomyelitis virus as to kill Escherichia coli. The amount of

chlorine now added to many city waters is not adequate to kill the poliomyelitis virus in 10 minutes. It is recommended that city water carries free chlorine residual of 0.15 to 0.30 ppm. Many rural well waters used by the public are contaminated with the E. coli group of bacteria. Three drops of laundry bleach (5.25% sodium hypochlorite solution), well mixed with one gallon of water was found adequate for chlorination of the few clear or only faintly turbid well waters tested.

FROM THE AUTHOR'S SUMMARY.

RISK OF PARALYTIC AND NONPARALYTIC FORMS OF POLIOMYELITIS TO HOUSEHOLD CONTACTS. MORRIS SIEGEL and MORRIS GREENBERG, J. A. M. A. **155**:429 (May 29) 1954.

The probability that more than one paralytic case will develop in a family is greater if the initial case is paralytic than when it is nonparalytic. Also the age span of susceptibility is increased.

If the initial case is paralytic, the subsequent cases have about a 70% chance of being paralytic.

KIMBALL, Evanston, Ill.

ANTIBODY RESPONSE TO A STIMULATING DOSE OF TETANUS TOXOID IN CHILDREN PREVIOUSLY IMMUNIZED WITH COMBINED DIPTHERIA AND TETANUS TOXOIDS (C.D.T.). SAUL WIENER, REGINALD W. PATTERSON, and E. FORBES MACKENZIE, M. J. Australia **1**:633-636 (April 30) 1955.

Six months after having received 2 doses of diptheria-tetanus toxoids, 64 children between the ages of 9 and 16 years were found to have had a protective level of tetanus antitoxin in their serum. The majority of these children had been previously immunized against diptheria.

Seven days after a "booster" dose of a prophylactic containing toxoid antibody levels indicated that adequate sensitization had occurred in every child.

McGUIGAN, Evanston, Ill.

CHANGES IN THE ELECTROENCEPHALOGRAPHIC RECORD FROM THIRTEEN CASES OF NONCOMPLICATED PERTUSSIS IN CHILDREN. E. BAULIEU and P. MISES, Presse méd. Supp. 53, p. 1113 (July 31) 1954.

The authors give the reasons why they have been led to carry out electroencephalographic investigations in whooping cough and to utilize either caffein in the cases where the paroxysmal cough prevails at night or bromide in the rarer cases, where the prevalence is diurnal.

They observed in the course of normal pertussis in children, such electroencephalographic abnormalities exclusively occurring in the course of the second, third, and fourth week of the paroxysmal period. During the same period those children who had been treated with caffein showed a normal electroencephalographic tracing. The occurrence of electroencephalographic abnormalities does not seem to be in relation to the number or intensity of paroxysms. They would disappear without leaving any electrical sequelae.

FROM THE AUTHORS' SUMMARY.

THE TREATMENT OF PERTUSSIS BY ACTH GIVEN INTRADERMALLY. N. POMPONIO, Lattante **25**:271 (May) 1954.

Twenty children, most of them under 2 years of age, were treated in the paroxysmal stage of pertussis by ACTH intradermally. The usual dose was 1.75 mg. daily. The number of paroxysms was found to diminish under this method of treatment. In the opinion of the author, this is the treatment of choice, provided the adrenal cortical function is normal.

HIGGINS, Boston.

THE USE OF ACTH AND CORTISONE TO COMPLEMENT ANTIBIOTICS IN SEPSIS. P. BONCOMPAGNI, E. NUCCI, and G. CELATA, Lattante **25**:728 (Nov.) 1954.

Two cases are reported of streptococcal infections, one a subacute bacterial endocarditis (aviridans Streptococcus) and the other an abdominal infection (Streptococcus faecalis), which did not respond to antibiotic therapy until it was complemented by ACTH-cortisone medication.

HIGGINS, Boston.

PURULENT MENINGITIS DURING TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN. N. POMPONIO, Lattante **26**:162 (March) 1955.

Six out of the last thirty-four patients undergoing treatment for tuberculous meningitis developed an acute purulent meningitis. In two of these cases, meningococci were the causative organisms, and recovery followed appropriate therapy. In the other four cases no causative organisms could be found in the spinal fluid; but in each the acute meningeal symptoms and the purulent spinal fluid were initiated by high fever, convulsions, and a red throat. Only one of these four patients recovered. In one of the cases, there were two recurrences of the fever and the spinal fluid findings before death occurred.

HIGGINS, Boston.

POLIOMYELITIS: EPIDEMIOLOGY AND PROPHYLAXIS—A STUDY OF THE EPIDEMIC OF 1954 IN BARCELONA. R. SALAS VASQUEZ, Arch. pediat. Barcelona **5**:359-397 (Jan.-Feb.) 1955.

The author writes in detail of the epidemiology and prophylaxis of poliomyelitis in general and gives specific data regarding the epidemiological characteristics of the 188 cases he personally treated.

Among the 188 paralytic cases 15.3% were preceded by an acute infection. Fourteen cases followed pertussis, and six followed measles. Trauma was present in 3.6%. Fatigue, traveling, and surgical intervention were not found in the history of this group.

Most of the children were between 1 and 2 years of age. The next age group having high frequency was between 2 and 3 years.

The seasonal incidence was the typical one for the northern hemisphere. There was no significance in sex distribution.

More city than rural people were stricken with the disease.

ALLEN, Santa Fe, N. Mex.

THE LUNGS IN WHOOPING COUGH. VLADIMAR KLUSKA and OLGA HANDSCHUHOVA, Pediat. listy **9**:211, 1954.

The tracheobronchial system is the main, primary site of specific clinical changes. Mediastinitis is characteristic for whooping cough. The basic histological feature is a peribronchial and perivascular mantle infiltration, characteristic for whooping cough.

The pulmonary segment and the corresponding bronchial supply represent an anatomical and functional unit, and the localization of the above changes in this system accounts for the quantitative and qualitative variety in the symptomatology of whooping cough.

The variability and diversity of the clinical picture in whooping cough is further conditioned by a series of functional changes. Pathophysiological research of whooping cough is essential.

FROM THE AUTHORS' SUMMARY.

Acute Infectious Diseases

ATYPICAL MUMPS MANIFESTATIONS, PARTICULARLY MUMPS MENINGOENCEPHALITIS. L. HLOUCAL and K. ŽÁČEK, Schweiz. med. Wchnschr. **85**:634-637 (June 25) 1955.

A 13-year-old girl with mumps had oophoritis and hepatitis, both of short duration. Hepatitis in mumps is rare.

AMBERG, Rochester, Minn.

THE EFFECT OF THE REMOVAL OF THE VACCINAL FOCUS ON THE ALLERGY TO TUBERCULIN IN GUINEA PIGS VACCINATED WITH PETRAGNINI'S ANATUBERCULIN WITH OR WITHOUT A DIFFUSING AGENT. L. C. SIGNORINI, Clin. pediat. **37**:207 (March) 1955.

Guinea pigs were given intradermal injections of a concentrated Petragnini's anatuberculin intradermally. In three different groups the site of the injection was excised surgically 1, 8, or 21 days later; at monthly intervals after the injections tuberculin tests were done. It was found that the time of appearance was sooner, the duration longer, and the intensity of the tuberculin reaction greater the longer the focus had been allowed to remain. However, when a diffusing agent, hyaluronidase, had been added to the anatuberculin, these differences were not found; this finding is probably due to the participation of other tissues and organs in developing the allergic response.

HIGGINS, Boston.

THE EFFECTS OF VACCINATION BY PETRAGNINI'S ANATUBERCULIN, WITH AND WITHOUT A DIFFUSING MEDIA, OF GUINEA PIGS INFECTED BY MYCOBACTERIUM TUBERCULOSIS. L. F. SIGNORINI and V. TERNI-PONS, Clin. pediat. **37**:275 (April) 1955.

Fifty-four guinea pigs were given injections of a human type tubercle bacillus. One group served as controls. To the other groups, at various times after the infection (1, 12, or 32 days), injections of anatuberculin were given either with or without the addition of hyaluronidase. Neither the weight curves nor the survival times were significantly different in the vaccinated and the unvaccinated animals. It is concluded that vaccination with anatoxin is ineffective on the course of experimental tuberculous infection in guinea pigs.

HIGGINS, Boston.

THE PROGNOSTIC VALUE OF CHLORIDE DETERMINATIONS IN CASES OF TUBERCULOUS MENINGITIS UNDERGOING TREATMENT. C. MARNI and M. P. PRODI, Clin. pediat. **37**:369 (May) 1955.

Every 8 days observations were made as to the chloride contents of the spinal fluid and the blood and as to the chloride excretion in the urine of 13 patients undergoing treatment for tuberculous meningitis. The patients who were in poor condition clinically were found to have low chloride contents in the blood and spinal fluid. Unless the patient was able to retain chloride in the body, the prognosis was very poor.

HIGGINS, Boston.

ACUTE INFECTIOUS LYMPHOCYTOSIS. F. FUMI and E. CLEMENTI, Clin. pediat. **37**:447 (June) 1955.

Five cases of acute lymphocytosis are reported in children. The white cell counts varied between 34,000 and 82,000, with 70% to 80% lymphocytes. Mild diarrhea was the usual initiating symptom which called attention to this mild disease. A moderate fever of a degree or two may follow a couple of days later. The lymphocytosis persisted for from 15 to 44 days. An estimate of 15 to 20 days is given as the incubation period. Aureomycin therapy had no effect toward lowering the lymphocyte counts.

HIGGINS, Boston.

A SEARCH FOR TUBERCLE BACILLI IN THE BONE MARROW, BLOOD, GASTRIC JUICE, AND SPINAL FLUID OF CHILDREN WITH TUBERCULOSIS. F. M. CHIOSSI and J. F. M. HÖLSCHER, Minerva pediat. **7**:582 (May 5) 1955.

Although tubercle bacilli could be cultured from the spinal fluids of almost all cases of tuberculous meningitis, the authors were unable to culture the bacteria from the blood, the bone marrow, or the gastric juice in any case of tuberculous meningitis, pleurisy, or primary pulmonary tuberculosis.

HIGGINS, Boston.

THE DIFFERENT TYPES OF C. DIPHTHERIAE FOUND ENDEMIC AND AS RELATED TO THE CLINICAL MANIFESTATIONS. C. CASCIO, Minerva pediat. **7**:744 (June 30) 1955.

The cultures from 92 children with diphtheria were found to be distributed into the following Anderson types: mitis 64%, intermedius 25%, grave 11%. The relative pathogenicity of these cultures was tested on guinea pigs and was found as would be expected from their names. The severity of the disease was found to be the same in children, regardless of the type of the organism. The location of the lesions was essentially the same with each type.

HIGGINS, Boston.

ELECTROENCEPHALOGRAPHY IN POLIOMYELITIS. G. CANAL, Minerva pediat. **7**:747 (June 30) 1955.

Electroencephalograms were made on 139 patients with poliomyelitis. The tracings were reported normal in 61 instances (44%), borderline in 48 (34%), and pathological in 30 (22%). The pathological findings were present in 50% of the tracings taken in the acute phase of the disease, in 17% of those taken one to 6 months after onset, in 19% of those taken 6 months to 1 year after, and in 30% of those taken after 1 year. Pathology was found in 15% of the tracings of children 1 to 3 years old, in 32% of tracings of children 3 to 7 years old, and in 38% of tracings of children 7 to 15 years old.

HIGGINS, Boston.

Demonstration of Diphtheriatoxins of Strains of Diphtheria Bacilli from Carriers in the Incubated Hen Egg. H. Knothe, Deutsche med. Wchnschr. **80**:785 (May 20) 1955.

Chicken embryos 9 to 10 days old are very sensitive to diphtheriatoxins. In this way toxin-forming bacilli can be differentiated. Non-toxin-producing stains and pseudodiphtheria bacilli grow in the incubated egg but do not kill the embryo. A number of strains (46) isolated from carriers were tested in guinea pigs and eggs. Of these, 33 gravis and 2 mitis type bacilli proved toxic in guinea pig and egg test, while 5 gravis and 3 mitis bacilli were only toxic in the egg test. Three of the mitis strains did not produce any toxin. For the demonstration of weekly toxic diphtheria bacilli the egg test is better than the guinea pig test.

Amberg, Rochester, Minn.

Clinical Experience in Children with Streptomycin of "Diminished Toxicity." K. Simon, Med. Klin. **50**:1022 (June 17) 1955.

It had been shown in animal experiments that a combination of streptomycin or dihydrostreptomycin with pantothenic acid does not lessen bacteriostatic activity, while the toxicity is diminished considerably. Fifty-seven children up to 4 years of age were treated with a combination for various forms of tuberculosis in addition to isoniazid or aminosalicylic acid. Lately only the dihydrostreptomycin pantothenate was used. Children below 5 years of age received a total of 20 to 30 gm. of dihydrostreptomycin, starting with daily doses of 20 mg/kg. During school age the maximum daily dose was 50 mg/kg. and a total of 40 gm. Children of more than 14 years of age (31) received at the most a total dose of 50 gm. A commercial preparation of dihydrostreptomycin pantothenate was employed in a 20% concentration. In spite of the high dosage, no neurological symptoms were noted. Once in 21 tests of cochlear function a slight effect was observed and no definite disturbance of vestibular function.

Amberg, Rochester, Minn.

Gastrointestinal Complications After Administration of Antibiotics in Children. Malte Kientiz, Med. Klin. **50**:1227-1229 (July 22) 1955.

Attention is called to Staphylococcus enteritis in children treated with antibiotics of broad spectrum activity, such as Aureomycin. In addition to nonspecific treatment, the administration of erythromycin is stressed.

Amberg, Rochester, Minn.

Chronic Infectious Diseases

Value of and Indications for the Induction of Pneumomediastinum in the Course of Primary Tuberculosis in Children. A. Breton, J. Mereau, and O. Dubois, Pédiatrie **10**:251, 1955.

Lymph nodes in the upper mediastinum and under the carina as well as mediastinal adhesions can be demonstrated by pneumomediastinum, which until now has been practiced only in adolescents and adults.

After sedation and relaxation through the administration of drugs, oxygen or filtered air is injected through the trachea or under the xyphoid process. The final pressure is kept below 20 to 25. The upper mediastinum and subcarinal region are explored by lateral tomography.

Glaser, Baltimore.

Proceedings of the Meeting on Pulmonary Tuberculosis in Children. Pédiatrie **10**: 303, 1955.

Six papers on the treatment of pulmonary tuberculosis in children are presented and followed by a discussion of the subject.

The discussion includes prognosis and treatment of pulmonary and osteoarticular tuberculosis, surgical and medical, during the first years of life as observed at six institutions, one of them in Spain, two in Belgium, and three in France.

Glaser, Baltimore.

The Blood Picture in Human and Experimental Mycosis. G. Gelli and I. Nieri, Minerva pediat. **7**:32 (Jan. 13) 1955.

A 10-year-old girl had a pulmonary mycosis due to Candida albicans. As the disease progressed, the total serum protein fell from 5.75 to 5.15 gm. per 100 cc., the albumin from 60.9%

to 39.6%, and the albumin/globulin ratio from 1.55 to 0.65; marked increases were found in the α_2-globulin (10.3% to 21.3%) and in the γ-globulin (18.5% to 32.1%). Rabbits inoculated by various Candida cultures showed an increase in the serum α_2-globulin but a definite fall in the serum γ-globulin.

HIGGINS, Boston.

Diseases of Blood, Heart and Blood Vessels, and Spleen

THERAPEUTIC AGENTS IN RHEUMATIC CARDITIS. BERTRAND L. STOLZER, HAROLD B. HOUSER, and ERNEST J. CLARK, A. M. A. Arch. Int. Med. **95**:677 (May) 1955.

The authors report their observations of 152 patients who were followed for 14 months subsequent to an acute attack of rheumatic carditis. The patients were divided into three approximately equal groups, each group receiving only one type of treatment during the acute phase. The three groups received, respectively, acetylsalicylic acid, cortisone, or corticotropin. The comparative effects of these drugs on the acute manifestations of rheumatic fever in these same patients have been presented elsewhere. No one drug employed exhibited marked advantages over the others in the treatment of the acute phase of rheumatic fever. The present study evaluates the comparative effects of these three drugs on rheumatic carditis as evidenced by the presence of murmurs during the 14-month period of observation. The fewest patients with significant murmurs at 14 months occurred in the cortisone-treated group, 18% in contrast with 34% in those patients treated with either of the other two drugs. It seemed that cortisone prevented the appearance of existing apical systolic murmurs and caused the disappearance of existing apical systolic murmurs during the treatment period to a greater degree than either acetylsalicylic acid or corticotropin. The authors point out that the differences observed among the three treatment groups do not allow a definite conclusion as to whether either of the steroid medications is superior to acetylsalicylic acid in the prevention of rheumatic valvular disease. However, they point out that the seemingly favorable effects of cortisone should prompt further investigation.

JONES, Chicago.

SPONTANEOUS REGRESSION OF ANGIOMAS IN CHILDREN. LEE BIVINGS, J. Pediat. **45**:643-647 (Dec.) 1954.

Simple angiomas of the hypertrophic type (strawberry mark) in infants regress spontaneously and seldom require treatment. Faintly marked squamous-cell angiomas regress slowly but almost completely. Port-wine angiomas do not regress; cosmetic covering is the best method of management. Cavernous angiomas require treatment but some of the simple subcutaneous masses will regress if given time. The spider type of angioma also seems to regress spontaneously.

MACDONALD, Pittsburgh.

STUDIES IN SICKLE CELL ANEMIA. ROLAND B. SCOTT, LELABELLE C. FREEMAN, and ANGELLA D. FERGUSON, Pediatrics **14**:209 (Sept.) 1954.

This survey of 1100 Negro children in various age categories was undertaken to determine the effect of age upon the appearance of the sickling phenomenon from infancy throughout childhood. The general incidence of sickling in 100 Negro children, including sickle-cell anemia and sickle-cell trait, was 7.4%. The data on the incidence of the asymptomatic sickling trait and of sickle-cell anemia are summarized by age and sex in tables.

The authors encountered 22 cases of sickle-cell anemia, seven of which were previously undiagnosed and unknown. Sixteen cases of sickle-cell anemia in boys and six in girls were encountered in the total test group, comprising 651 boys and 449 girls.

This investigation disclosed 60 subjects bearing the asymptomatic sickling trait. There were 40 and 20 instances of asymptomatic sickling observed in 635 boys and 443 girls, respectively. When the sexes were divided into two age categories (1 month through 4 years and 5 years through 16 years), there was an actual decrease in the incidence of sickling in the girls and an increase in the sickling phenomenon in the boys. We have no explanation for this finding. The over-all incidence of the sickling trait for both sexes in all age groups represents no significant deviation from a 1 : 1 ratio.

The data available from this study failed to disclose a definite progressive increase in the incidence of sickling in the age groups studied. Quantitatively the general transition from the low incidence of sickling in the newborn (3.4%) to the higher occurrence in older children

(7.5%) apparently takes place during the first year of life. Additional studies of both a qualitative and quantitative nature and involving a detailed age breakdown during the first year of life would probably elucidate this period of transition. AUTHORS' SUMMARY.

CALCIFICATION OF THE ARTERIES IN INFANCY AND CHILDHOOD. W. A. COCHRANE and D. H. BOWDEN, Pediatrics **14**:222 (Sept.) 1954.

Eight cases of calcification of the arteries have been described, six infants and two older children. The arterial lesions in all are similar, consisting of a deposit of calcium on the internal elastic lamina followed by more extensive calcification and fibrous thickening of the intima. The etiology of the infantile condition is unknown. The lesions in the older children are probably secondary to renal disease. FROM THE AUTHORS' SUMMARY.

UNUSUAL ROENTGEN MANIFESTATIONS OF PATENT DUCTUS ARTERIOSUS. ALEXANDER R. MARGULIS, MELVIN M. FIGLEY, and AARON M. STERN, Radiology **63**:334-345, 1954.

An uncomplicated patent ductus presents a fairly uniform roentgen appearance, dominating by dilatation of the pulmonary artery. Frequently in young adults the heart is of normal shape, whereas in congestive failure in infants all chambers are enlarged. In some there is a selective left ventricular enlargement.

The authors present seven cases with unusual and instructive roentgen findings. These important roentgen signs are (1) pulmonary infarction due to bacterial endarteritis, (2) calcification in the aortic origin of the ductus (authors' case age 29), (3) dilatation of the descending aorta at the origin of the ductus—the infundibulum of the patent ductus arteriosus, (4) angiocardiographic "jet defect" in the pulmonary artery, (5) reversed shunt through the ductus due to pulmonary hypertension demonstrable by angiocardiography (authors' case 5), (6) unusual heart shape in infancy (authors' case age 4), (7) aneurysm of the pulmonary artery (authors' case age 4).

Angiocardiography seldom demonstrates the ductus directly as does aortography. The authors describe the indirect signs and suggest the order of specificity. They believe that the "jet defect" in the pulmonary artery is quite specific for patent ductus, but similar defects may be seen in other anomalous communications, such as ventricular septal defect and an anomalous insertion of the pulmonary veins. ANSPACH, Riverside, Ill.

SOME PULMONARY CHANGES ASSOCIATED WITH INTRACARDIAC SEPTAL DEFECTS IN INFANCY. KENNETH L. KRABBENHOFT and WILLIAM A. EVANS JR., Radiology **63**:498-507 (Oct.) 1954.

Associated pulmonary atelectasis and/or emphysema were found in 86% of patients with interatrial septal defects, in 50% with combined atrial and interventricular defects, and in 22% with isolated interventricular lesions, while only 5.5% had these changes in transposition of the vessels.

The authors believe that chondromalacia (absence of cartilage rings), flaccidity of the cartilage, and squamous-cell metaplasia are possible causes of the pulmonary changes. The cases studied did not exhibit abnormal viscid mucus of fibrocystic disease of the pancreas or mucoviscidosis. Neither did they show the usual signs of bronchiolitis or asthma.

The authors conclude that the presence of persistent and progressive signs of atelectasis and/or emphysema, if variable, in an infant with a cardiac murmur, is strong indication of an intracardiac and probably an interatrial defect.

Dr. Holt in discussing this paper added significantly that a large percentage of patients dying with septal defects have pneumonitis with associated atelectasis and emphysema than in other congenital cardiac defect and called attention to the fact that the cardiac defects with largest pulmonary blood supply have the largest incidence of infection.

ANSPACH, Riverside, Ill.

BACTERIAL ENDOCARDITIS COMPLICATING SEPTICAEMIA IN AN INFANT. IAN C. LEWIS, Arch. Dis. Childhood **29**:144 (April) 1954.

This case had the characteristic signs of septicemia. The infection appeared to be staphylococcal, as this organism was grown from the umbilicus, and Gram-positive cocci in clusters were seen in the section of the mitral valve vegetation.

The infant apparently responded to antibiotics, and when he was discharged from hosptial no cardiac abnormality was suspected. The clinical picture on his readmission four days later was that of congestive heart failure. The cause of the symptoms was only discovered at the postmortem examination, when the size and situation of the endocardial vegetation showed that there must have been intermittent obstruction of the mitral orifice.

KELLY, Milwaukee.

HAEMOGLOBIN AND RED CELLS IN THE HUMAN FOETUS: II. THE RED CELLS. ELIZABETH P. N. TURNBULL and JAMES WALKER, Arch. Dis. Childhood **30**:102 (April) 1955.

The red cells in the cord blood of the human fetus have been studied from the 10th to the 43d weeks of pregnancy. The packed cell volume, the mean cell diamenter, and the reticulocyte count have been measured and the absolute values of the red cell characteristics calculated.

As pregnancy progresses the red cells as a whole become more mature. The Price-Jones curve shifts to the left, the base narrows, and the peak becomes higher.

Three groups of cells have been studied in detail; 9μ and over, 8 and 8.5μ, 7.5μ and under.

It is shown that as pregnancy progresses the number of cells less than 9μ in size in each unit volume of blood gradually increases, while the numbers which are 9μ and over remain nearly unchanged. There is, however, in the later weeks a wide variation in the number of large and small cells in the blood of different infants.

Deficiency of oxygen supply to the fetus in the later weeks of pregnancy alters the red cell pattern from that seen under normal conditions of growth and maturation.

KELLY, Milwaukee.

HAEMOGLOBIN AND RED CELLS IN THE HUMAN FOETUS: III. FOETAL AND ADULT HAEMOGLOBIN. JAMES WALKER and ELIZABETH P. N. TURNBULL, Arch. Dis. Childhood **30**:111 (April) 1955.

The proportion of adult hemoglobin has been measured in the blood of the human fetus from the 10th to the 43d week of pregnancy. Adult hemoglobin was first detected at the 13th week and rose until, at the 22d to 24th weeks, 10% of the hemoglobin was adult. After the 35th week the proportion of adult hemoglobin rose steadily, and at 42 weeks a mean value of 30.7% was found.

The rise in the proportion of adult hemoglobin is primarily a function of the growth and maturation of the fetal tissues, and in the well-oxygenated fetus in the late weeks production of fetal hemoglobin steadily lessens.

The extra hemoglobin produced in the late weeks under the stimulus of anoxia is mainly or entirely of the fetal type.

KELLY, Milwaukee.

BLOOD FORMATION IN INFANCY: PART III. CORD BLOOD. JOHN MARKS, DOUGLAS GAIRDNER, and JANET D. ROSCOE, Arch. Dis. Childhood **30**:117 (April) 1955.

From analyses of cord blood from a large series of infants normal hematological values have been derived.

The normal cord blood hemoglobin level ranges from 12 to 22 gm. per 100 ml. No relationship between cord blood hemoglobin and fetal maturity was found.

The hemoglobin level at 7 weeks and 9 weeks of age was determined in two groups of infants: (*a*) those born with a high normal cord hemoglobin and (*b*) those born with a low normal cord hemoglobin. At 2 months of age each group had a similar hemoglobin level of about 11 gm./100 ml.

KELLY, Milwaukee.

THE DETERMINATION OF BLOOD PRESSURE IN INFANTS BY THE FLUSH METHOD. JOHN REINHOLD and MICHAEL PYM, Arch. Dis. Childhood **30**:127 (April) 1955.

The flush method is a simple and accurate means for determining the systolic blood pressure in infants. The method is described and is shown to give reproducible results. The gradient of systolic blood pressure between the arms and legs in 27 normal newborn and older infants is recorded. In many the pressure in the legs was lower than that in the arms, but in none was this difference greater than 14 mm. of Hg, and in the majority it was considerably smaller.

This contrasts with the findings in adults (Hamilton, Woodbury, and Harper, 1936) where the systolic pressure in the femoral artery has been shown to be 20 mm. of Hg higher than that in the brachial.

In two infants with coarctation of the aorta of the adult type the systolic pressure in the legs measured by the flush method was 52 mm. and 40 mm. of Hg less than that in the arms.

KELLY, Milwaukee.

BLOOD FORMATION IN INFANCY: PART IV. THE EARLY ANAEMIA OF PREMATURITY. DOUGLAS GAIRDNER, JOHN MARKS, and JANET D. ROSCOE, Arch. Dis. Childhood **30**:203 (June) 1955.

The early anemia of premature infants is due mainly to the slow response of erythropoiesis to the stimulus of anemia.

This slow response is not peculiar to premature infants, but in them its consequence is exaggerated by the rapidity of their growth.

Rapid growth also has the effect of prolonging the anemia once this has developed.

There is no evidence that an abnormal rate of red cell destruction, if it occurs, contributes significantly to the production of anemia.

Marrow studies reveal no differences between the myelograms of premature and normal infants.

Iron, if given from about the third week, mitigates the anemia but does not always prevent it. Iron is well tolerated, and there seems good reason to give it to the smaller premature infants from about the third or fourth week.

If cobalt is given in addition to prophylactic iron, a striking increase in erythropoiesis can be provoked, sufficient in most cases to prevent anemia from developing. However, the effects which cobalt may have upon the thyroid make it unjustifiable to administer it routinely to premature infants.

KELLY, Milwaukee.

THE SCHÖNLEIN-HENOCH SYNDROME (ANAPHYLACTOID PURPURA) COMPARED WITH CERTAIN FEATURES OF NEPHRITIS AND RHEUMATISM. IAN C. LEWIS, Arch. Dis. Childhood **30**:212 (June) 1955.

A series of cases of the Schönlein-Henoch syndrome, acute hemorrhagic glomerulonephritis, and acute rheumatism have been compared with regard to sex ratio, age of onset, seasonal trends, and the incidence of previous upper respiratory tract infections, particularly those associated with the hemolytic Streptococcus.

It is suggested that the evidence supports a close relationship between the Schönlein-Henoch syndrome and acute nephritis and a bacterial hypersensitivity as a major etiological factor in all three conditions.

KELLY, Milwaukee.

THE CLINICAL ASSESSMENT OF HAEMOLYTIC DISEASE OF THE NEWBORN. KAREL POLACEK, Arch. Dis. Childhood **30**:217 (June) 1955.

Common methods of assessing the severity of hemolytic disease of the newborn, before and after birth, are briefly discussed. Hemoglobin and bilirubin concentrations in cord blood are taken as the chief criteria of severity. Exchange transfusion is performed (1) when the cord hemoglobin concentration is below 12 gm/100 ml., (2) when the hemoglobin is above 12 gm/100 ml. and the cord bilirubin concentration exceeds 3 mg/100 ml., when the Coombs test is positive in premature infants. By these criteria, exchange transfusion was indicated in 46 newborn infants (5 deaths, no cases of kernikterus in survivors). On the other hand, their reliability has allowed a conservative attitude to be taken without any harm in 31 Rh-positive infants of isoimmunized mothers.

KELLY, Milwaukee.

THE DENTAL CHANGES ASSOCIATED WITH KERNIKTERUS. R. FORRESTER and JOHN MILLER, Arch. Dis. Childhood **30**:224 (June) 1955.

In 13 cases of kernicterus following hemolytic disease an acute enamel hypoplasia of the deciduous teeth was observed. Similar lesions were found in nine premature infants who had developed cerebral palsy; these cases are tentatively cited as examples of "kernikterus of prematurity."

Similar but milder enamel lesions have been found in normal premature infants but not in full-term children in the absence of kernicterus.

The cause of the enamel lesion is not established, but it is suggested that the elucidation of this problem may throw some light on the cause of the damage to the central nervous system. Attention is drawn to the diagnostic value of these changes in cases of cerebral palsy or congenital deafness.

KELLY, Milwaukee.

ON A SEARCH FOR RHESUS ANTIBODIES IN VERY YOUNG FOETUSES. BRUCE CHOWN, Arch. Dis. Childhood **30**:232 (June) 1955.

Two Rh-positive fetuses of sensitized Rh-negative women were examined. In the first case the mother had an anti-Rh albumin antibody with a titer of 2. The fetus was about 10 weeks old. No antibody could be demonstrated in its blood or tissue fluids. In the second case the mother had a titer of 64; the fetal cells were direct-Coombs positive; the serum contained anti-Rh albumin antibody. A portion of the amniotic fluid of the latter fetus was palely yellow.

KELLY, Milwaukee.

CHRONIC CONSTRICTIVE PERICARDITIS COMBINED WITH HYPOPROTEINAEMIA. F. KUIPERS, Arch. Dis. Childhood **30**:285 (June) 1955.

A case is presented of constrictive pericarditis in a 7-year-old boy, demonstrating some atypical signs. Hypoproteinemia and ascites were dominating. No complaints or signs of heart failure were present, with the exception of increased venous pressure, as could be demonstrated in the neck. The radiokymograph showed fair pulsations of the ventricles, but the data on the pressure curves from the right auricle, right ventricle, and pulmonary artery gave definite evidence of constrictive pericarditis. The presence of calcium in the pericardium could be demonstrated only on pictures taken with "hard" x-rays.

A successful pericardectomy and epicardectomy (nearly total) was done, which was followed by restoration of the blood proteins in three weeks.

The association of hypoproteinemia and constrictive pericarditis in childhood was commented upon.

KELLY, Milwaukee.

SKIN CHANGES IN RETICULOENDOTHELIOSIS WITH SPECIAL RELATION TO ABT-LETTERER-SIWE'S DISEASE. HANS GUNTER NOLLER, IRMA WAGNER, and CONRAD BODENSTEDT, Ann. paediat. **183**:145 (Sept.) 1954.

Observation made on an infant of 4 weeks with Abt-Letterer-Siwe's disease in whom characteristic histological and morphological skin manifestations dominated the clinical picture from birth made us investigate the occurrence of such manifestations in the reticuloendothelioses. The specific signs were found in the majority of the Abt-Letterer-Siwe cases, and they are not rare in lipid granulomatosis, in Hand-Schuller-Christian's disease, and in some of the other leukemic or aleukemic reticuloendothelioses.

FROM THE AUTHORS' SUMMARY.

APLASTIC ANEMIA (CHRONIC ERYTHROBLASTOPHTHISIS) DUE TO AUTOIMMUNIZATION. R. E. BONHAM-CARTER, I. A. B. CATHIE, and C. GLASSER, Schweiz. med. Wchnschr. **84**:1114 (Sept. 25) 1954.

A boy about 5 years of age was seen in an acquired hemolytic attack which responded to an intensive treatment with cortisone combined with transfusions and antibiotics. A year later, following a familial catarrhal infection, a severe anemia developed. In addition to cortisone and ACTH treatment, a splenectomy was done. During the attacks, the presence of erythrocyte antibodies could be demonstrated in the serum. It is concluded that acquired hemolytic anemias can proceed to aplastic or pseudoaplastic anemias. Destruction or disturbed maturation of the erythrocytic series can occur by means of activity of abnormal constituents in the patient's plasma. In the presence of aplastic anemia, previous or still-existing hemolytic processes are to be considered. If this is the case, treatment with cortisone or ACTH and splenectomy are indicated.

AMBERG, Rochester, Minn.

A Congenital Heart Condition—with Pulmonary Veins Entering the Right Auricle, an Open Interauricular Septum, and Malformation of the Tricuspid Valve—Complicated by Rheumatic Pancarditis. E. Miceli, Clin. pediat. **36**:253 (April) 1954.

A 14-year-old boy was diagnosed as having a congenital malformation of the heart when he was less than 1 year old; he subsequently had frequent episodes of bronchopneumonia, with dyspnea, cyanosis, and cardiac enlargement. At the age of 13 years, he had acute rheumatic fever with pancarditis. He died 18 months later.

The necropsy findings were congenital heart abnormalities, including an interauricular opening due to incomplete development of the septum, openings of the pulmonary veins into the right auricle, an abnormal tricuspid valve, hypoplasia and stenosis of the aorta; rheumatic pancarditis, with an enlarged and decompensated heart and a pericarditis; chronic bronchitis, and bronchopneumonia.

The entry of the pulmonary veins into the right auricle is a rare congenital anomaly; previously reported cases of this condition are listed together with the other congenital anomalies found in each case.

Higgins, Boston.

Bone Lesions in Leukemia in Children. C. Montanelli and G. Visentin, Clin. pediat. **36**:695 (Sept.) 1954.

X-ray pictures showing periosteal and cortical lesions in the bones of three children with acute lymphatic leukemia illustrate the frequency with which the bones are involved in this disease.

Higgins, Boston.

Reflections on Rheumatic Carditis, Suggested by Some Reports Presented at the Fourth Inter-American Congress of Cardiologists. G. Costa Bertani, Lattante **25**:257 (May) 1954.

An Argentinian cardiologist summarizes some of the highlights of rheumatic fever as brought out at the recent congress in that country. The large number of cases has resulted in the social aspects of the disease being stressed; much active study along this line is being done in Uruguay. The general concensus of opinion was that about 30% of the children with rheumatic fever do not have cardiac involvement. The use of cortisone for this disease should still be subject to rigorous scientific as well as clinical control.

Higgins, Boston.

Three Cases of Cardiac Insufficiency in Babies. G. Scalamogna and G. Zarbin, Minerva pediat. **6**:116 (Feb. 28) 1954.

The cases of three children, 1 to 2 years old, with similar findings of acute cardiac failure are reported. The onset was rapid, and there were tachycardia, polypnea, cardiac enlargement, and hepatomegaly; but there were no fever or electrocardiographic changes. In each of these cases, oxygen and cardiokinetic drugs led to the return of normal cardiac function within a few days. In general, the prognosis of acute cardiac failure in small children must, however, be guarded, as any of several etiological agents may be responsible for the cardiac failure.

Higgins, Boston.

The Hemoglobin Metabolism in Patients with Congenital Heart Pathology Before and After Surgical Intervention. M. Malaspina, P. Nicola and A. Actis, Minerva pediat. **6**:180 (March 31) 1954.

The hemoglobin metabolism of 18 children with congenital malformation of the heart, 16 of them with cyanosis, was studied by blood hemoglobin determinations and a quantitative evaluation of the excretion of biliary pigments. It was found that the excretion of biliary pigments closely paralled the hemoglobin percentage in the blood. Following surgical operations in eight cases and relief of the cyanosis, there was a marked increase in the urinary and fecal excretion of the biliary pigments at the time of the hemolytic crisis as the blood hemoglobin percentage rapidly fell.

Higgins, Boston.

SOMATOTROPIC HORMONE (STH) AND THE BLOOD PICTURE. P. SFORZINI and M. NEGRI, Minerva pediat. **6**:645 (Aug. 31) 1954.

Eleven children, three under 1 year and eight between 2 and 9 years of age, were given between 10 and 30 units of STH (the lyophilic somatotropic hormone, Choay) daily for from five to eight days. In about one-half of the cases there was produced a mild leucocytosis and in the other half a definite lymphocytosis. The hormone had no effect on the red blood cell count the reticulocyte count, or the platelet count in any of the cases except two. These two children were recovering from a tuberculous infection; their blood cell count and Hgb. increased following the taking of the hormone; the STH may have acted to overcome a maturation block in the bone marrow caused by the antituberculosis drugs the children had received.

HIGGINS, Boston.

THE LIPOPROTEINS IN THE SERA OF NORMAL CHILDREN. G. GELLI, Minerva pediat. **6**:868 (Nov. 15) 1954.

Determinations were made of the percentages of the various lipoproteins (α_1, α_2, β_1 and β_2) in the sera of 40 children of various ages. Electrophoretic methods were used.

HIGGINS, Boston.

SUBACUTE RETICULOENDOTHELIOSIS WITH A HIGH BLOOD LEVEL OF PHOSPHATIDES IN AN INFANT. A. GENTILI and M. LOPEZ, Pediatria **62**:1 (Jan.) 1954.

An apparently normal 6-month-old infant developed on his body a hemorrhagic, eczema-like dermatitis; this was followed by enlargements of the lymph nodes, liver, and spleen, anemia, leucocytosis, and fever; terminally he became jaundiced and had dyspnea, dying at the age of 12 months.

He had a marked lipemia, due mainly to excessive amounts of phosphatides. The lymph nodes contained an abundance of reticulohistiocytes, containing material taking the Sudan stain. The skin also was invaded by histiocytes, which, however, contained no fatty material.

HIGGINS, Boston.

THE RELATION OF FETAL HEMOGLOBIN AND CARBONIC ANHYDRASE IN THE RESPIRATORY EXCHANGE IN THE NEWBORN AND THE NURSING INFANT. S. CUTILLO, Pediatria **62**:209 (March) 1954.

It was found that the larger the amount of fetal hemoglobin, the lower was the amount of carbonic anhydrase in the blood of infants. This finding seems to explain why the physiology of the respiratory exchange is different in the newborn and very young infants from that in the older infant.

HIGGINS, Boston.

THE FREQUENCY OF THE STIGMATA OF FALCEMIO (SICKLE-CELL ANEMIA) AMONG HEALTHY CHILDREN IN SICILY. L. VALENTINO and V. LUNA, Pediatria **62**:547 (July) 1954.

The sickle-cell trait was found in 8 out of 5000 children (0.16%) from various parts of Sicily, as the result of blood tests by the Itano-Pauling method.

HIGGINS, Boston.

EFFECT OF O_2 THERAPY ON WHITE CELLS IN LEUKEMIA. R. COCCHI, Riv. clin. pediat. **53**:352 (Nov.) 1954.

The author describes the findings obtained with oxygen therapy by inhalation methods on number of circulating white cells per cubic millimeter during leukemia.

FROM THE AUTHOR'S SUMMARY.

DIAGNOSIS OF CONGENITAL CARDIOPATHIES—TRICUSPID ATRESIA. J. M. DURAN ANDREU, Arch. pediat., Barcelona **5**:299-309 (Jan.-Feb.) 1955.

The author describes the anatomy of the heart in tricuspid atresia with diagnostic data from the clinical and x-ray viewpoints. The electrocardiogram may not be very helpful, but the x-rays will be very typical.

He discusses the prognosis and concludes that if the pulmonary circulation is also deficient the Taussig-Blalock operation may be the treatment of choice.

ALLEN, Santa Fe, N. Mex.

ADDITIONAL TREATMENT OF FETAL ERYTHROBLASTOSIS WITH PERISTON N. G. MARTIUS and F. PREDIGER, Deutsche med. Wchnschr. **80**:1134-1137 (Aug. 5) 1955.

For reasons given, Periston N. was injected intravenously twice daily, 10-15 ml/kg., in addition to exchange transfusions, leading to an increase of urine elimination. The urine contained bile pigment. Fourteen of fifteen erythroblastic infants survived; an infant with hydrops universalis could not be saved. For further details the paper is to be consulted.

AMBERG, Rochester, Minn.

APLASTIC CRISIS IN CONSTITUTIONAL HEMOLYTIC ICTERUS: SIMULTANEOUS ILLNESS OF THREE SISTERS IN CONNECTION WITH A GRIPPE INFECTION. K. BETKE, F. BEBATIN AND R. SAUTHOFF, Deutsche med. Wchnschr. **80**:1358-1360 (Sept. 16) 1955.

Three sisters, aged 2, 7, and 8 years, became ill with grippe, which provoked an aplastic crisis in a previously not recognized constitutional hemolytic anemia. The infectious agent was with high probability influenza virus B.

AMBERG, Rochester, Minn.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

CONGENITAL DUODENAL OBSTRUCTION: A CLINICAL ROENTGENOLOGICAL, SURGICAL AND FOLLOW-UP STUDY IN TWENTY-NINE CASES. SIGURD EEK, American J. Roentgenol. **73**:713-733 (May) 1955.

This article correlates the clinical and radiographic findings in 29 cases of congenital duodenal obstruction. The article is most complete and has excellent roentgenograms and line drawings explaining the mechanism and the occurrence of the various types of obstruction. The obstructions are classed as follows:

1. Intrinsic duodenal obstructions—comprising 5 cases
   (*a*) Diaphragmatic or veil obstruction
   (*b*) Canal stenosis
   (*c*) Atresia
2. Extrinsic duodenal obstructions—comprising 24 cases
   (*a*) Malrotation
   (*b*) Anular pancreas

The author concludes that (1) the violence of the manifestation of congenital, organic duodenal obstruction is proportional to the degree of the stenosis present; (2) if the cause of the obstruction acts permanently, the clinical manifestation is the same, whether the stenosis is extrinsic or intrinsic; (3) the volvulus in cases of malrotation of the intestine is, as a rule, intermittent; the first attack may come at any age but is commonest in the neonatal period; (4) persons with malrotation of the intestine should never overload the intestines with large quantities of food and/or fluids.

He also concludes that the choice of the surgical procedure used did not influence the late result, provided the obstruction was relieved.

ALTMAN, Miami, Fla.

CARCINOMA OF THE COLON IN CHILDHOOD. CARRINGTON WILLIAMS JR., Ann. Surg. **139**:816 (June) 1954.

Carcinoma of the colon is a rare disease in children under 16 years of age. About 50 cases of carcinoma of the colon in children have been reported. The author reports three additional cases.

The symptoms of colonic carcinoma in childhood are distressingly nonspecific. Pain is the outstanding feature and may indicate beginning intestinal obstruction. Nausea and vomiting are common. Bleeding is very unusual. The possibility of carcinoma of the colon should be considered in the differential diagnosis of children with abdominal pain where the diagnosis is in doubt, particularly with chronic or recurrent spells of abdomnal pain.

The treatment of choice is radical resection of the colon with restoration of the bowel continuity.

The prognosis with these lesions is extremely poor, the longest recorded survival being only four years postoperatively.

BANTIN, Omaha.

PORTAL CAVAL ANASTOMOSIS IN INFANTS. HENRY G. HOLLENBERG and BARNEY P. BRIGGS, Ann. Surg. **141**:648-652 (May) 1955.

Some remarks regarding portal hypertension in infants are presented. It is suggested that the condition may be commoner than is ordinarily recognized.

There are two crucial questions about this matter which immediately arise. First, can the surgical relief of portal hypertension aid in reversing a cirrhotic process in the liver? The authors feel that it does, but they really do not know. Second, when should one elect to perform this major procedure upon a patient who has been doing reasonably well? The authors favor operation as early as one can be sure that the situation is progressive and before it becomes advanced.

BANTIN, Omaha.

UNUSUAL ABDOMINAL CYSTS IN INFANTS AND CHILDREN. NEWLIN HASTINGS and WILLIAM J. NORRIS, California Med. **81**:84 (Aug.) 1954.

In a 20-year period at the Childrens Hospital of Los Angeles 46 infants and children have had operations for cysts within the abdomen. The age range of patients was from newborn to 13 years. Most of them were under 4 years old. There were four general groups of these cysts: 1. About one-half were cysts of the ovary, some of them serous and some dermoid. These cysts are attached by a stalk that often twists, causing gangrene or rupture with acute symptoms simulating appendicitis. 2. Next in frequency were cysts arising in the mesentery of the intestine. They usually caused little trouble until by their size (up to a 2 qt. capacity) they created pressure and obstruction in the intestine. 3. Enteric cysts were found in four patients. 4. Cysts of the pancreas were present in three of the children.

X-ray examination was helpful in diagnosis. Usually the type of cyst was not determined until operation was done. Transection of the intestinal tract sometimes was necessary for removal of the cyst. Surgical correction was satisfactory in 44 of the 46 cases.

PRYOR, Redwood City, Calif.

MODERN TREATMENT OF HIRSCHSPRUNG'S DISEASE. ORVAR SWENSON, J. A. M. A. **154**:651 (Feb. 20) 1954.

Unless there is a dramatic narrowing over a distance of 8 to 10 cm. with marked dilatation of the colon above, the diagnosis of Hirschsprung's disease cannot be made. Also there must be a history of being constipated since birth. If the patients are to be treated surgically, they should have a complete procedure, which consists of removing all of the aganglionic colon.

KIMBALL, Evanston, Ill.

GAMMA GLOBULIN: EFFECT ON SECONDARY ATTACK RATES IN INFECTIOUS HEPATITIS. ALTA ASHLEY, New England J. Med. **250**:412 (March 11) 1954.

Serum globulin was effective in reducing the incidence of secondary cases among family contacts of patients with infectious hepatitis. The secondary attack rate in families receiving no inoculation was 15.2%, while that in families protected by globulin was 0.6%.

Family size was a factor influencing the secondary attack rate.

The highest over-all attack rate (primary and secondary) occurred in children of school age in the general population and in the 235 families studied; schools were often cited as probable sources of infection.

WHEELOCK, Denver

GAMMA GLOBULIN IN PREVENTION OF INFECTIOUS HEPATITIS: STUDIES ON USE OF SMALL DOSES IN FAMILY OUTBREAKS. DAVID YI-YUNG HSIA, MAURICE LONSWAY JR., and SIDNEY S. GELLIS, New England J. Med. **250**:417 (March 11) 1954.

Gamma-globulin in a dosage of 0.01 cc. per pound of body weight was given to alternate members of 40 families; in each of these families a sporadic case of infectious hepatitis had developed.

Only one case of hepatitis occurred among 38 exposed adults and 57 exposed children who were given γ-globulin. Jaundice was noted six days after injection in that case.

In contrast, secondary cases appeared in 2 of the 55 exposed adults (4%) and 11 of 40 exposed children (27%) who were the untreated controls within the same families.

Administration of 0.01 cc. per pound of body weight appears to be as effective as that of 0.1 cc. in preventing the spread of infectious hepatitis within family groups.

WHEELOCK, Denver.

MECONIUM PERITONITIS. FRANK J. RIGOS, Northwest Med. **53**:695 (July) 1954.

The author discusses the possible causes, symptoms, sequelae, and differential diagnosis of meconium peritonitis. Three case reports, with roentgenograms illustrating the characteristic intraperitoneal calcifications, are presented.

DOCTER, Seattle.

ANORECTAL RINGS IN INFANCY: INCIDENCE AND SIGNIFICANCE. LLOYD E. HARRIS, H. PENUEL, F. CORBIN, and JOHN R. HILL, Pediatrics **13**:59 (Jan.) 1954.

Anorectal rings were found in 13.8% of 1716 consecutive newborn infants. The anorectal ring was detected in four times as many girls as boys.

Anorectal rings of the grades discovered in this study dilated spontaneously and did not require treatment.

The incidence of constipation, colic, blood in the stool, excessive straining, distention, tear of the anal skin, and crying with defecation was the same in a group of 168 infants with anorectal rings as it was in a group of 160 infants in whom the anorectal ring was absent.

A thick, fibrous anorectal ring which does not dilate spontaneously may cause obstructive symptoms and require treatment. This type of anorectal ring did not occur in this group of 1716 infants.

FROM THE AUTHORS' SUMMARY.

INVESTIGATION OF AN INFANT BORN OF A MOTHER SUFFERING FROM CIRRHOSIS OF THE LIVER. ROBERT L. SLATER, Pediatrics **13**:308 (April) 1954.

The successful pregnancy and uncomplicated delivery of a healthy infant by a young woman suffering from severe cirrhosis of the liver is described.

Serial liver function studies in the infant during the neonatal period suggested a degree of hepatic immaturity not dissimilar to that observed in normal newborn infants.

Maternal serum alterations are compared with fetal and neonatal findings. Electrophoretic analysis revealed that the fetus had a normal albumin concentration, despite a low level in the mother. The serum γ-globulin was elevated in the fetus, just as it was in the mother. Serum bilirubin was present in only half the concentration in the fetus as it was in the mother. Differences in lipoproteins and in other high molecular weight components were found. The role of placental permeability in relation to these variations is discussed.

Serial electrophoretic analyses during the neonatal period indicated a normal catabolic rate for the unusually elevated γ-globulin component in the infant (half-life=20 days; $t\frac{1}{2}$= 20 days).

FROM THE AUTHOR'S SUMMARY.

GASTROESOPHAGEAL INCOMPETENCE IN CHILDREN, WITH SPECIAL REFERENCE TO MINOR DEGREES OF PARTIAL THORACIC STOMACH. ROY ASTLEY and IVO J. CARRÉ, Radiology **62**:351 (March) 1954.

Weakness of the valve mechanism between the esophagus and stomach, allowing abnormal reflux of stomach contents into the gullet in infancy and early childhood, is not an infrequent cause of vomiting. The process is facilitated by the horizontal posture and fluid diet. In the authors' experience, a short esophagus with a small proportion of the stomach above the diaphragm occurs as a cause of vomiting more often than does cardioesophageal relaxation (chalasia), recognized as a frequent cause of vomiting. Often the pinchcock action of the right crus of the diaphragm is not effective; the obliquity of the esophagus is lost, and there results a wide hiatus. While vomiting is the outstanding feature, commonly blood altered in character and in small amounts and mucus in large quantities are present.

Treatment in infancy consists of nursing in a propped-up position. Thickened feedings are given if vomiting persists. Dysphagia for solid food is predominant when a complicating stricture is present.

ANSPACH, Riverside, Ill.

SUBACUTE AND CHRONIC INTUSSUSCEPTION IN INFANTS AND CHILDREN. DUNCAN MACAULAY and THOMAS MOORE, Arch. Dis. Childhood **30**:180 (April) 1955.

Two cases of intussusception in infants, of prolonged duration, four and six weeks respectively, are reported in detail.

From an analysis of hospital records it is concluded that the incidence of prolonged intussusception is about 3% of all cases in infants under one year of age and about 10% in children over that age. These figures are in substantial agreement with those derived from a review of the literature.

Subacute and chronic intussusception in infants and children is not such a rare condition as is often claimed.

KELLY, Milwaukee.

PRIMARY TUMORS OF THE LIVER IN CHILDREN. L. MARTONI and F. BRILLANTI, Clin. pediat. **36**:3 (Jan.) 1954.

Three cases of primary tumors of the liver in children 8 to 10 years old are reported. One tumor was a cirrhotic cancer, the second an adenocarcinoma, and the third an adenoma. In the latter all the signs and symptoms were localized, the child showing neither loss of weight nor anemia. There appeared to be evidences of malignancy in that the cells were invading the blood vessels of the tumor itself. The diagnosis in each case was established histologically after exploratory operations.

HIGGINS, Boston.

UNUSUAL CASE OF RIGHT-SIDED DIAPHRAGMATIC HERNIA. C. MONTANELLI and S. BIANCHESSI, Clin. pediat. **36**:47 (Jan.) 1954.

A 29-month-old boy had had a poor appetite and frequent febrile attacks since birth. He was very pale and asthenic and subject occasionally to diarrhea and occasionally to constipation. He was normal mentally. Physical and x-ray exminations revealed a diaphragmatic hernia, part of the stomach being in the right thorax and part in the abdomen. The spleen was not enlarged. Gastric analyses showed abundant free hydrochloric acid. There was occult blood in the stools. The anemia was of the macrocytic and hypochromic type and was doubtless due to bleeding in the stomach.

HIGGINS, Boston.

PERFORATING APPENDICITIS IN CHILDHOOD. HEINZ SINGER, Deutsche med. Wchnschr. **79**:110 (Jan. 15) 1954.

During a period of four years, 3020 children up to 14 years of age came to operation on suspicion of appendicitis. Among these were 131 children with perforation of the appendix. There seemed to be an increase of perforations in children below the age of 5 years, with a peak in the 3d year of life. Diagnosis and treatment are discussed. In the course of the observation period, the mortality dropped from 8% to 0.

AMBERG, Rochester, Minn.

INFECTIOUS GASTROENTERITIS OF INFANTS DUE TO "PATHOGENIC" COLIN ORGANISMS. LIS MOSER, Deutsche med. Wchnschr. **79**:355 (Feb. 26) 1954.

In a home for mothers joined to the University Children's Clinic in Hamburg, 10 of 20 infants were taken ill. In nine of these cases, so-called pathogenic colin bacteria of the O-Group 55 (Kauffmann) could be demonstrated in the stools. The differentiation of these micro-organisms, which rests on serological examinations, is discussed. The outbreak is ascribed to an error, inasmuch as for a few days the diapers had not been boiled. A possible carrier was found.

AMBERG, Rochester, Minn.

THE RELATIONSHIP BETWEEN INFECTIOUS ENTERITIS DUE TO ESCHERICHIA COLI AND THE ACUTE DIARRHEAS OF INFANCY. CHRISTEL JUNKTE, Monatsschr. Kinderh. **103**:253-261 (May) 1955.

The question of the relationship of infectious enteritis due to Escherichia coli to the entire picture of the acute infantile diarrheas, parenteral infections, and to the so-called parenteral dyspepsias was studied.

All infants admitted to the Children's Hospital of the German city of Magdeburg during 11 consecutive months of 1953 had repeated stool examinations for the presence of the following

pathogenic types of E. coli: 0111: B_4, 055: B_5, 026: B_6 and 025: K. All patients who developed dyspepsia during their hospital stay also had stool examinations. A total of 5700 stool examinations was performed on 1500 infants, of whom 1331 were followed from the time of admission until discharge.

Pathogenic types of E. coli were found in 11.6% of infants admitted with dyspepsia with parenteral infections and in 9.3% of infants who developed their illness while in the hospital. Of infants admitted with dyspepsia without parenteral infection 32% had pathogenic types of E. coli, and 74.2% who developed their illness while in the hospital were found to have pathogenic types of E. coli.

No significant relationship was found between parenteral infection and the occurrence of E. coli enteritis during winter months. The etiology of summer diarrhea and vomiting could not be explained on the basis of E. coli dyspepsia, as there was a marked and significant rise of E. coli enteritis during the winter months. This winter increase was found only in infants already hospitalized and not in new admissions.

E. coli types 0111: B_4 and 055: B_5 were most frequently found in epidemics, whereas 026: B_6 was never found in outbreaks but only in a few contact infections.

Sixty per cent of E. coli dyspepsias occurring during hospitalization took place during the first three weeks after admission. Serum agglutination studies and blood cultures were negative. Pathogenic types of E. coli were found in throat cultures but not in catheterized urine specimens and purulent ear drainage. Pathogenic types of E. coli were found on many objects in the rooms of patients as well as on hands of nurses even immediately after washing.

HARTENSTEIN, Syracuse, N. Y.

EFFECT OF HEPATITIS DURING PREGNANCY ON THE CHILD. H. ELLEGAST, G. GUMPESBERGER, and F. WEWALKA, Wien. klin. Wchnschr. **66**:507 (July 23) 1954.

Of 57 cases of hepatitis during pregnancy a placental transmission of hepatitis to the child could be assumed in only one instance, which is reported. Of 25 cases in which the mother acquired a hepatitis during or a few weeks after birth, one infant died at the age of 6 months with an acute liver atrophy. When the mothers of 43 infants had hepatitis, 12 in the first, 16 in the second, and 15 in the third period of pregnancy, no malformations of the infants were seen.

AMBERG, Rochester, Minn.

VIRUS DIARRHEA IN INFANTS. S. DREXLER and V. KUBELKA, Pediat listy **9**:43 (June) 1954.

The authors report on an epidemic of diarrhea, probably of virus origin, in premature babies. A virus was isolated which, they believe, could have been the cause of the epidemic. Evidence is presented to show that the infection took place by droplets or the alimentary route. Chloromycetin, and possibly Aureomycin, are recommended by way of treatment.

FROM THE AUTHORS' SUMMARY

Psychology and Psychiatry

CLINICAL PSYCHOLOGY IN CONGENITAL ENCEPHALOPATHIES. J. DE MORAGAS, Rev. espan. pediat. **11**:62 (March-April) 1955.

It must be remembered in considering the use of clinical psychology in encephalopathies that (1) an encephalopathy may exist without any sign of psychopathology; (2) the psychopathology which accompanies an encephalopathy is not always significant of an oligophrenia; (3) the psychological signs which accompany an encephalopathy are not necessarily due to the same nosogenic agent that produced the encephalopathy; (4) some of the psychological signs accompanying an encephalopathy are not due to the effect of the encephalopathy on the patient but due to reaction to his lesion and to his environment.

The author elaborates these points and stresses especially the concept of oligophrenia as an entity to be distinguished from symptomatic signs and symptoms mistaken for oligophrenia in children with brain damage.

ALLEN, Santa Fe, N. Mex.

Diseases of Ductless Glands; Endocrinology

EFFECT OF A PITUITARY GONADOTROPHIN ON OVARIES OF HYPOTHYROID RATS. RALPH G. JANES, Endocrinology **54**:464 (April) 1954.

It has been shown that thyroidectomy or the administration of goitrogenic substances is followed by changes in the ovary. These observations suggest that, in the absence of normal thyroid function, the ovaries react abnormally to the circulating gonadotropins. The present experiments are concerned with the effects of varying doses of a gonadotropin on animals which were given a goitrogen or were thyroidectomized for different periods of time.

It was found that thyroidectomy results in an increased response to gonadotropin and that the ovarian weights in some instances are even greater than in the thiouracil-treated. The increased ovarian response to gonadotropin is a qualitative, rather than a quantitative, effect and is apparently caused by a luteinizing rather than a follicular-stimulating factor.

JACOBSEN, Buffalo.

EFFECTS OF ACTH ON PREGNANT MONKEYS AND THEIR OFFSPRING. IDA G. SCHMIDT and RICHARD A. HOFFMAN, Endocrinology **55**:125 (Aug.) 1954.

In view of the likelihood that, for various reasons, ACTH would be administered during pregnancy, it seemed desirable to define the effects of such treatment on mother and offspring. Accordingly, this investigation of the effects of ACTH on the pregnant rhesus monkey and her offspring was carried out.

Three of the seven pregnant treated monkeys aborted. The other four pursued an uneventful course and gave birth to apparently healthy offspring. Maternal spleens and lymph nodes showed characteristic suppression of activity in the nodules. These same organs in the babies were unaffected, but the thymus glands showed cortical atrophy.

Maternal adrenals responded typically to ACTH by hypertrophy of fascicular cells and loss of vacuolation in the cytoplasm. Fetal adrenals, on the contrary, were very small, with enlarged glomerular zones and atrophic fascicular zones—changes similar to those produced in adult adrenals by cortisone. This suggested that excessive amounts of cortical steroids from the enlarged maternal adrenals passed into the fetal circulation and inhibited activity of fetal adrenals.

JACOBSEN, Buffalo.

ROLE OF THE KIDNEY IN PARATHYROID CONTROL OF BLOOD CALCIUM AS DETERMINED BY STUDIES ON THE NEPHRECTOMIZED DOG. ARTHUR GROLLMAN, Endocrinology **55**:166 (Aug.) 1954.

Despite numerous studies, the mechanism of the action of the parathyroid hormone remains a subject of controversy. The view which has received widest acceptance considers the primary action of the parathyroid hormone to be exerted by accelerating the excretion of phosphate through the kidney with secondary effects on the calcium level of the blood. Opposed to this view is a mass of data which indicates that the parathyroid hormone also exerts significant extrarenal effects, particularly on the bones, which are responsible for its hypercalcemic action.

The present study demonstrates that parathyroid hormone acts directly on body stores of calcium (presumably the bones, but perhaps also on the tissues) to regulate the calcium level of the blood and that the hypercalcemic action of the hormone is not dependent on its renal action in increasing phosphate diuresis. This is proved by the demonstrated capacity of the hormone to cause hypercalcemia in the nephrectomized dog, even when the total inorganic phosphate of the blood is rising, as well as by the decrease in serum calcium and the induction of tetany in the parathyroidectomized-nephrectomized dog.

JACOBSEN, Buffalo.

EFFECT OF CORTICOIDS UPON THE DEVELOPMENT AND TOXICITY OF TRANSPLANTABLE CROTON-POUCH TUMORS. HANS SELYE, Endocrinology **56**:516-522 (May) 1955.

The growth and systemic toxicity of transplanted "croton-pouch tumor No. 2" (a highly malignant fibrochondro-osteosarcoma) was examined in intact and in adrenalectomized rats treated with Cortisol, DCA, or both these steroids.

It was found that cortisol greatly inhibits both the growth and the exudate-forming ability of croton-pouch sarcomas, but only in the absence of adrenal tissue.

These findings suggest that DCA imitates the Cortisol-antagonizing effect of intact adrenal tissue in many respects.

JACOBSEN, Buffalo.

Books

BOOKS RECEIVED

Our Blind Children. By Berthold Lowenfeld. Price, $5.50. Pp. 205, with 4 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

Introduction to Virology. By Gilbert Dalldorf. Price, $3.50. Pp. 102. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

Clinical Laboratory Diagnosis. Ed. 5. By Samuel A. Levinson and Robert P. MacFate. Price, $12.50. Pp. 1246, with 257 illustrations. Lea & Febiger, 600 Washington Sq., Philadelphia 6, 1956.

The Psychopathology of Children with Organic Brain Disorders. By Lauretta Bender. Price, $5.50. Pp. 151, with 23 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

Mechanisms of Congenital Malformation. By S. R. M. Reynolds, Joseph Dancis, and Clement A. Smith. Price, $3. Pp. 137, with 50 illustrations. Association for the Aid of Crippled Children, 345 E. 46th St., New York, 1955.

BOOK REVIEWS

Therapy of Fungus Diseases—An International Symposium. Edited by Thomas H. Sternberg and Victor D. Newcomer. Price, $7.50. Pp. 337, with numerous tables. Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

Fifty-five papers presented at an international symposium in June, 1955, are included. With their illustrations and figures they provide an up-to-date review as well as a forward-looking summary of the world's knowledge of fungus infections, particularly with regard to therapy. Much previously unpublished information is presented on the recently established antifungal antibiotic Nystatin, as well as other antifungal agents, including Diphenylpyraline, undecylenic acid, sulfur, aromatic diamidines, cinnamic acids, Nitrostyrenes, Filipin, sulfonamides, sulfones, Chlorquinaldol, 1968, Actidione, stilbamidines, MRD-112, Rhodanine, and others. Biological aspects of superficial and deep fungus infections are also discussed from many points of view. The editors and publishers deserve praise for the prompt appearance of the volume.

To pediatricians the very favorable reports on Nystatin in pediatrics by Drouhet, of Paris, and by Dobias, of the U. S. A., are of special interest, for they suggest that this agent is the treatment of choice in cutaneous or mucosal or systemic moniliasis in infants and children.

A Handbook of Hospital Psychiatry. By Louis Linn. Price, $10. Pp. 560. International Universities Press, Inc., 227 W. 13th St., New York 11, 1955.

Dr. Louis Linn, assistant attending psychiatrist at Mt. Sinai Hospital, New York, has written this book to help the resident psychiatrist or beginning psychiatrist in his approach to the mental patient in the hospital setting with accent on the team approach and importance of the "therapeutic community." The book fulfills its purpose admirably and contains a wealth of fairly detailed information which will serve to guide the psychiatrist in innumerable situations.

The first of its five sections, "The Treatment Program," deals in a general way with various forms of therapy that are used in a hospital. Included are individual psychotherapy, group psychotherapy, somatotherapy, recreational therapy, occupational and vocational therapy, food as therapy, and special ward procedures. The second section deals with the treatment team and takes up in quite some detail the role and training of the social worker, psychologist, attendant, nurse, chaplain, and volunteer worker. This material is helpful not only in outlining the function of each group but in helping to understand the interrelationship between the groups. Section

three deals with the various types of patients in the mental hospital. They are approached from all aspects, the psychology involved, the various forms of treatment and research. Special problems such as pregnancy in patients and physical illness are also considered. Part four deals with the hospital as to architecture and once again with staff, specifically administrative and psychiatric. Again training and function are discussed in detail. Many helpful details in regard to training and research grants are given. The last part deals with the community and its relationship to psychiatry and the mental patient. The role of relatives, their education and treatment, is discussed, as is that of continued outpatient care for discharged patients. Education of the public in mental health is included, and various agencies and their programs are discussed.

There is a wealth of useful information in this volume, and it will be a valuable addition to anyone in any way involved with psychiatric patients in the hospital setting or after discharge.

Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man. By Harvey Blank, M.D., and Geoffrey Rake, M.B., B.S. Price, $8.50. Pp. 285, with 70 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

An unusually happy combination of clinical and laboratory experience have combined to produce a very valuable book. Factual, authoritative, and very up to date, this book will be of value to medical students, clinicians, and laboratory workers. The style of presentation is lucid and interesting, and the book is excellently illustrated. The clinician will find detailed descriptions of laboratory aspects of each disease which are informative as to laboratory methodology as well as virus properties. The laboratory worker will find accurate thorough discussions of the clinical aspects of these diseases.

Discussions of pox diseases, exanthemata, and warts are particularly good. The authors have endeavored to discuss the less common virus diseases of man as well as those commonly encountered in everyday experience.

While the discussions of some of the rarer diseases are brief and sketchy, the disappointment is in the current extent of our knowledge rather than in the authors' efforts to assemble what is known. Therapeutic discussions are limited to those measures which are specific, and only pertinent nonspecific measures are included.

The authors have devoted much of their attention to the viral diseases. It is disappointing that the same meticulous care was not given to the rickettsial diseases. Nonetheless, this book will be a valuable asset to both the clinical and the laboratory worker dealing with infectious diseases. All pediatricians will find it a most useful and handy source of reference.

Sexual Hygiene and Pathology. By John F. Oliven, M.D. Price, $10. Pp. 481. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1955.

There is an increasing awareness among physicians of the medical importance of sex matters. In the present day, people are entitled to informed physicians who know the answers to personal health and hygiene questions as well as to problems on the subject of sex when the need for advice and treatment arises.

This original book is organized into four sections "Sexuality in Childhood"; "Sexuality in the Second Decade"; "Sexuality of the Normal Adult"; and "Sexual Pathology." The material dealing with the first, second, and fourth categories will be reviewed here. This volume was originally conceived following a Round Table on the Sex Instruction of the Medical Student by members of the American Psychiatric Association and under their auspices. This was developed further by the author in having selected physician friends keep a record of the sexual problems which happened to come to their professional attention, as well as to suggest information they would like to have in this field. In so doing, Dr. Oliven has kept close to the viewpoint of the practicing physician. There is enough theoretical data to facilitate the use of this volume as an adequate reference and as a textbook for teaching purposes.

In the section on "Sexuality in Childhood," the normal and abnormal sexual development of the child is fully portrayed, with an elaboration of the modern concept of sex instruction and common sex problems of the child. The area of sexual aggression of the child, an experience which comes to every physician from time to time, is adequately discussed as to the legal and psychiatric sequelae. This discussion alone is worthy of the pediatrician having this book ever at hand, so that he will not flounder about when it is his role to speak and act authoritatively.

"Sexuality in the Second Decade" is a most important discussion for those who have been meagerly trained in the modern concepts of this important age level. Normal and abnormal

puberal development is detailed, with a sensible approach to adolescent sex education, as well as to a discussion of the common sex problems and disordered sex behavior in juveniles. Here again the physician, disoriented by the welter of quasiscientific material in this field, will find a forte and adequate background for his opinion.

The section on "Sexual Pathology" is effectively organized and defined in terms which any physician can comprehend and helps to dispel the confusion of the concepts and labels which have constantly besieged this field. It is trite to say that a physician must be well informed in the pathology of any phase of medicine before he may adequately deal with the prevention and correction of deviations.

The facile choice of technical terms which are readily understandable and the extreme readability of the textual material are highly commendable. There is a complete index, and the use of cross references throughout the text increases its usefulness to the reader. Although there is no appended bibliography, one has the impression that the author is well steeped in the lore of his field, and his forthright exposition leaves one with the security that he writes with a liberal background of other than his own personal convictions.

This book is recommended to all physicians and medical social workers dealing with adolescents and certainly should be a reference volume in every good law library.

The Importance of Physiotherapy in the Treatment of Sick Children. By J. M. Jewry-Harbert. Price, $2.50. Pp. 84, with 15 illustrations. John de Graff, Inc., 64 W. 23d St., New York 10, 1955.

This small monograph is designed to help the physiotherapist understand the peculiar needs of children regarding physiotherapy. The author feels there is a lack of specialized knowledge in this field and has therefore put down her own impressions after an extended experience in the field of physiotherapy with infants and young children. A special section of exercises for babies is included.

Polio Pioneers. By Dorothy and Philip Sterling. Price, $2.75. Pp. 128, with numerous illustrations. Doubleday & Company, Inc., 575 Madison Ave., New York 22, 1955.

This small volume is designed for lay reading at the secondary school level. Its lucid text and many excellent photographs make this an outstanding book for this purpose. It can be recommended highly for the families, the patients themselves, or others interested in the story of polio.

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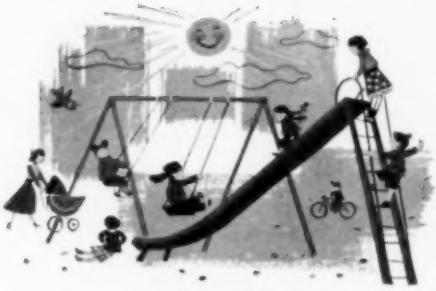

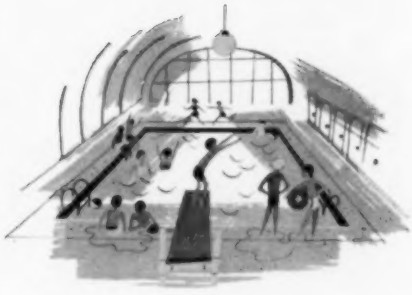

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1. Johnson, S. H., III, and Marshall, M., Jr.: A.M.A. Am. J. Dis. Child. 89:199, 1955. 2. Brookey, R. S.; Holt, S. H., and Siegel, D.: J. Michigan M. Soc. 54:805, 1955.

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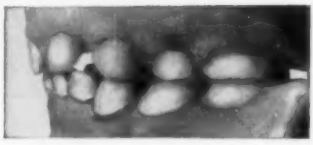

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1. Martin, E. A.: Roberts' Nutrition Work with Children Chicago, The University of Chicago Press, 1954, pp. 164-195.
2. Widdowson, E. M., and McCance, R. A.: Studies on the Nutritive Value of Bread and on the Effect of Variations in the Extraction Rate of Flour on the Growth of Undernourished Children, Medical Research Council, Special Report Series, No. 287, London, Her Majesty's Stationery Office, 1954.
3. Sherman, H. C.: Food Products, ed. 4, New York, The Macmillan Company, 1948, p. 221.

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†Protein	4.7 Gm.	3.9 Gm.	8.6 Gm.	†Iron	1.28 mg.	0.12 mg.	1.40 mg.
Carbohydrate	17.7 Gm.	5.7 Gm.	23.4 Gm.	†Calcium	15 mg.	148 mg.	163 mg.
Fat	2.0 Gm.	4.4 Gm.	6.4 Gm.	†Phosphorus	115 mg.	113 mg.	228 mg.
†Thiamine	0.18 mg.	0.05 mg.	0.23 mg.	Potassium	162 mg.	163 mg.	325 mg.
†Niacin	0.26 mg.	0.10 mg.	0.36 mg.	Zinc	1.08 mg.	0.45 mg.	1.53 mg.
†Riboflavin	0.05 mg.	0.19 mg.	0.24 mg.	Folic acid	11.4 mcg.	0.3 mcg.	11.7 mcg.
†Pyridoxine	0.07 mg.	0.06 mg.	0.13 mg.	Vitamin B_{12}	0.1 mcg.	0.7 mcg.	0.8 mcg.
Pantothenic acid	0.25 mg.	0.41 mg.	0.66 mg.	†Copper	0.31 mg.	0.04 mg.	0.35 mg.
†Vitamin A plus Carotenoids	—	0.08 mg.	0.08 mg.	Manganese	1.45 mg.	0.002 mg.	1.45 mg.
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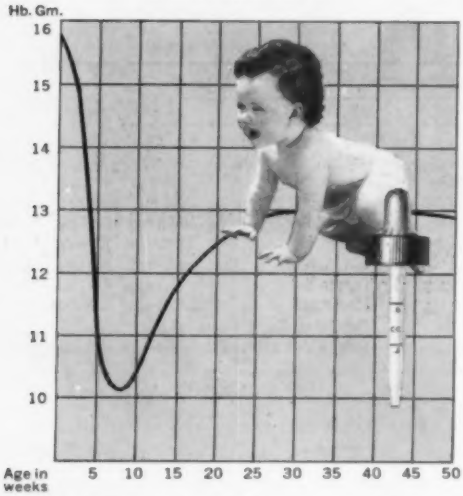

Chart adapted from Niccum, Jackson and Stearns: A.M.A. Am. J. Dis. Child. 86: 553, 1953.

Mean hemoglobin determinations of infants on a predominantly milk diet receiving Fer-In-Sol. The Fer-In-Sol dose was 5 mg. of iron (0.2 cc.) per day at 3 months, increased to 10 mg. of iron (0.4 cc.) after 6 months of age.[1]

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iron in a drop for infants and children

"Iron deficiency anemia has a peak incidence between six months and two and one-half years..."[2]

Smith and Rosello[3] found that the peak incidence of iron deficiency in infants and children occurred between the ages of 6 and 24 months, when growth is most rapid. Sturgeon[4] reports that published data indicate iron deficiency in infants is common. Although consuming normal diets, the majority of infants in the last half of the first year of life, and throughout the second year of life, "exist in relatively severe states of iron deficiency (30% or more depleted)."[4]

Niccum, Jackson and Stearns[1] found that prophylactic administration of Fer-In-Sol in small daily doses "was sufficient to maintain hemoglobin values at a constant level throughout the latter half of infancy in all full term infants"... resulted in significantly higher hemoglobin values than did ferric ammonium citrate.

FER-IN-SOL

Fer-In-Sol® provides a pleasant way to supply ferrous sulfate—a well tolerated, well absorbed and efficiently utilized form of iron. The vehicle is acidulous to improve absorption and utilization. The good taste of the solution makes it readily acceptable to young children. And tolerance is good.

Only 0.3 cc. of Fer-In-Sol supplies 7.5 mg. of iron—more than the Recommended Daily Allowance for children up to 4 years old. Fer-In-Sol is supplied in 15 cc. and economical 50 cc. bottles, with the new calibrated 'Safti-Dropper' of unbreakable plastic.

(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86: 553, 1953. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 155, 1954. (3) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1: 375, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

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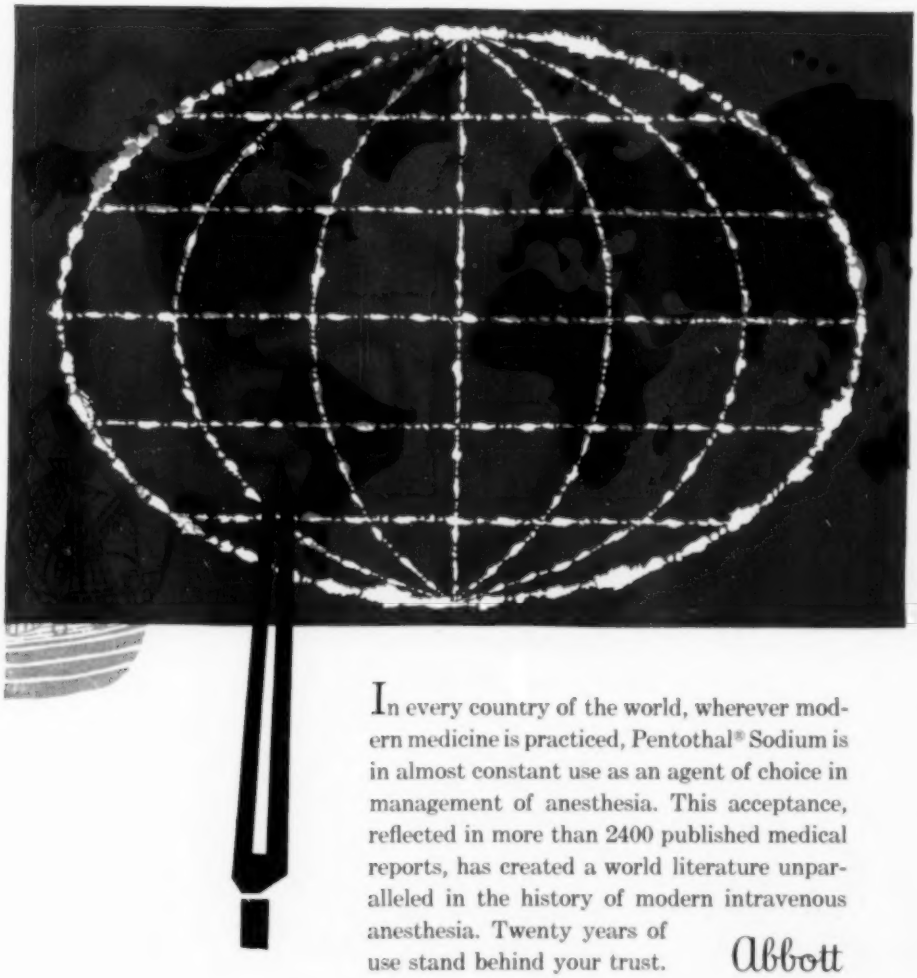

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